L6 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:56367 CAPLUS
DOCUMENT NUMBER: 130:76182
TITLE: Methods and compositions for the rapid and enduring relief of inadequate myocardial function
INVENTOR(S): Seed, Brian; Seed, John C.
PATENT ASSIGNEE(S): Heart Care Partners, USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5861399	A	19990119	US 1996-680684	19960717
US 6159993	A	20001212	US 1998-198874	19981124

PRIORITY APPLN. INFO.: US 1996-680684 A1 19960717

AB Disclosed are methods and compns. for reducing coronary artery **stenosis**, restoring blood flow to infarcted myocardium, improving myocardial perfusion, reducing heart attacks or other adverse cardiovascular events, or treating symptoms of inadequate myocardial function in a mammal involving administering to the mammal (a) a compd. that includes eicosapentaeneoic acid or docosahexaeneoic acid and (b) a **cholesterol**-lowering therapeutic, combined with dietary restrictions (resulting in aggressive loading of marine lipids), whereby a serum LDL concn. of less than 75 mg/dL (and preferably less than 55 mg/dL) is achieved. One particular method involves administering to the mammal a combination that includes (a) a compd. that includes an eicosapentaeneoic or docosahexaeneoic acid (for example, a marine lipid) and (b) a **cholesterol** synthesis or transfer inhibitor, and which may also optionally include aspirin and/or niacin. The methods and compns. of the invention may also further include a bile acid sequestrant and/or buspirone. Also disclosed are methods for treating heart disease that involve administration of buspirone.

REFERENCE COUNT: 2
REFERENCE(S): (1) Anon; Conn's Current Therapy 1992, P205
(2) Breivik; 1987 CAPLUS

L6 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:147517 CAPLUS
DOCUMENT NUMBER: 116:147517
TITLE: Phencyclidine and phencyclidine metabolite assays, tracers, immunogens, antibodies and reagent kit
INVENTOR(S): Dubler, Robert Edward; Frintner, Mary Pat; Grote, Jonathan; Hawksworth, David James; Nam, Daniel S.; Wray, Larry Kay; Hadley, Gregg Allen; Hopkins, Hal Dayton; Ungemach, Frank S.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: Eur. Pat. Appl., 34 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 459387	A2	19911204	EP 1991-108674	19910528
EP 459387	A3	19920902		
EP 459387	B1	19950920		

R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL

US 5155212	A	19921013	US 1990-529988	19900529
AU 9177272	A1	19911205	AU 1991-77272	19910522
AU 643524	B2	19931118		
CA 2043372	AA	19911130	CA 1991-2043372	19910528
AT 128241	E	19951015	AT 1991-108674	19910528
ES 2080188	T3	19960201	ES 1991-108674	19910528
JP 04235199	A2	19920824	JP 1991-125955	19910529
US 5407834	A	19950418	US 1992-831762	19920427

PRIORITY APPLN. INFO.: US 1990-529988 19900529
US 1986-866193 19860521

OTHER SOURCE(S): MARPAT 116:147517

AB The present invention is directed to a fluorescence polarization assay for phenylcyclidine and phenylcyclidine derivs., to the various components needed for prepg. and carrying out such an assay, and to methods of making these components. Specifically, tracers, immunogens and (monoclonal) antibodies are disclosed, as well as methods for making them, and a reagent kit contg. them. The tracers and the immunogens are made from substituted phencyclidine compds. A fluorescein moiety is included in the tracer, while a poly(amino acid) forms a part of the immunogen. The assay is conducted by measuring the degree of polarization retention of plane polarized light that has been passed through a sample contg. antiserum and tracer. The assay has a high degree of specificity for phencyclidine and metabolites and analogs thereof, while minimizing mass reactivity to a host of other synthetic metabolites and naturally occurring compds.

L6 ANSWER 3 OF 5 USPATFULL

ACCESSION NUMBER: 2000:168040 USPATFULL

TITLE: Methods and compositions for the rapid and enduring relief of inadequate myocardial function

INVENTOR(S): Seed, Brian, Boston, MA, United States
Seed, John C., Princeton, NJ, United States

PATENT ASSIGNEE(S): Heart Care Partners, Princeton, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6159993		20001212
APPLICATION INFO.:	US 1998-198874		19981124 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-680684, filed on 17 Jul 1996, now patented, Pat. No. US 5861399

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jordan, Kimberly
LEGAL REPRESENTATIVE: Clark & Elbing LLP
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
LINE COUNT: 993

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are methods and compositions for reducing coronary artery **stenosis**, restoring blood flow to infarcted myocardium, improving myocardial perfusion, reducing heart attacks or other adverse cardiovascular events, or treating symptoms of inadequate myocardial function in a mammal involving administering to the mammal (a) a compound that includes eicosapentaeneoic acid or docosahexaeneoic acid and (b) a **cholesterol**-lowering therapeutic, combined with dietary restrictions (resulting in aggressive loading of marine lipids), whereby a serum LDL concentration of less than 75 mg/dl (and preferably less than 55 mg/dl) is achieved. One particular method involves administering to the mammal a combination that includes (a) a compound that includes an eicosapentaeneoic or docosahexaeneoic acid (for example, a marine lipid) and (b) a **cholesterol** synthesis or transfer inhibitor, and which may also optionally include aspirin and/or niacin. The methods and compositions of the invention may also further include a bile acid sequestrant and/or buspirone. Also disclosed are

methods for treating heart disease that involve administration of buspirone.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 5 USPATFULL

ACCESSION NUMBER: 95:34082 USPATFULL

TITLE: Phencyclidine and phencyclidine metabolites assay, tracers, immunogens, antibodies and reagent kit

INVENTOR(S): Dubler, Robert E., Gurnee, IL, United States
Frintner, Mary P., Elk Grove, IL, United States
Grote, Jonathan, Grayslake, IL, United States
Hadley, Gregg A., St. Louis, MO, United States
Hawksworth, David J., Vernon Hills, IL, United States
Hopkins, Hal D., Chicago, IL, United States
Nam, Daniel S., Lake Elsinore, CA, United States
Ungemach, Frank S., Lake Villa, IL, United States
Wray, Larry K., Highland Park, IL, United States

PATENT ASSIGNEE(S): Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5407834		19950418
APPLICATION INFO.:	US 1992-831762		19920427 (7)

RELATED APPLN. INFO.: Division of Ser. No. US 1990-529988, filed on 29 May 1990, now patented, Pat. No. US 5155212 which is a continuation-in-part of Ser. No. US 1986-866193, filed on 21 May 1986, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kim, Kay K. A.
LEGAL REPRESENTATIVE: Pope, Lawrence S.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 32 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1662
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a fluorescence polarization assay for phencyclidine and phencyclidine derivatives, to the various components needed for preparing and carrying out such an assay, and to methods of making these components. Specifically, tracers, immunogens and antibodies are disclosed, as well as methods for making them, and a reagent kit containing them. The tracers and the immunogens are made from substituted phencyclidine compounds. A fluorescein moiety is included in the tracer, while a poly(amino acid) forms a part of the immunogen. The assay is conducted by measuring the degree of polarization retention of plane polarized light that has been passed through a sample containing antiserum and tracer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 5 OF 5 USPATFULL

ACCESSION NUMBER: 92:84969 USPATFULL

TITLE: Phencyclidine and phencyclidine metabolites assay, tracers, immunogens, antibodies and reagent kit

INVENTOR(S): Dubler, Robert E., Gurnee, IL, United States
Frintner, Mary P., Elk Grove, IL, United States
Grote, Jonathan, Grayslake, IL, United States
Hadley, Gregg A., St. Louis, MO, United States
Hawksworth, David J., Vernon Hills, IL, United States
Hopkins, Hal D., Chicago, IL, United States
Nam, Daniel S., Lake Elsinore, CA, United States
Ungemach, Frank S., Lake Villa, IL, United States

	Wray, Larry K., Highland Park, IL, United States		
PATENT ASSIGNEE(S):	Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5155212		19921013
APPLICATION INFO.:	US 1990-529988		19900529 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1986-866193, filed on 21 May 1986, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Nucker, Christine		
ASSISTANT EXAMINER:	Kim, Kay K.		
LEGAL REPRESENTATIVE:	Breininger, Thomas M.		
NUMBER OF CLAIMS:	3		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	32 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	1511		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a fluorescence polarization assay for phencyclidine and phencyclidine derivatives, to the various components needed for preparting and carrying out such an assay, and to methods of making these components. Specifically, tracers, immunogens and antibodies are disclosed, as well as methods for making them, and a reagent kit containing them. The tracers and the immunogens are made from substituted phencyclidine compounds. A fluorescein moiety is included in the tracer, while a poly(amino acid) forms a part of the immunogen. The assay is conducted by measuring the degree of polarization retention of plane polarized light that has been passed through a sample containing antiserum and tracer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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     FILE 'REGISTRY' ENTERED AT 11:34:19 ON 17 DEC 2001
                  E BUSPIRONE/CN
L1             2 S E3-E5
                  E NIACIN/CN
L2             1 S E3

     FILE 'CAPLUS, BIOSIS, USPATFULL' ENTERED AT 11:37:25 ON 17 DEC 2001
L3            11 S L1 AND L2
L4            10 DUP REM L3 (1 DUPLICATE REMOVED)
L5         56058 S L4 AND CHOLESTEROL OR STENOSIS
L6             5 S L4 AND (CHOLESTEROL OR STENOSIS)
L7            17 S L1 AND (CHOLESTEROL)

=>
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Iacoviello K, Amore C, De Curtis A, et al. Modulation of fibrinolytic response to venous occlusion in humans by a combination of low-dose aspirin and n-3 polyunsaturated fatty acids. *Arterioscler Thromb.* 1992;12(10):1191-1197.

Kooijmans-Coutinho MF, Rischen-Vos J, Hermans J, Arndt JW, van

Arterosclerosis, Thrombosis, + Vascular Biology

American Journal of Cardiology
1996, 77:31-36
Eritsland et al
Effect of dietary supplementation of n-3
fatty acids on coronary ...

Circulation 84-6
2588-2590
1991
Vane et al

all ordered
12-17-01

Possible Interactions with: Docosahexaenoic Acid (DHA)

Also listed as: DHA

In combination with aspirin, omega-3 fatty acids could be helpful in the treatment of some forms of coronary artery disease. Consult your healthcare provider about whether this combination would be appropriate for you if you have coronary artery disease.

Omega-3 fatty acids may reduce some of the side effects associated with cyclosporine therapy, which is often used to reduce the chances of rejection in transplant recipients. Consult your healthcare provider before adding any new herbs or supplements to your existing medication regimen.

In an animal study, omega-3 fatty acids protected the stomach against ulcers induced by reserpine and nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin. Consult your healthcare provider before using omega-3 fatty acids if you are currently taking these medications.

Top

Drug Interactions

- Aspirin
- Aspirin-containing Medications
- Cyclosporine
- Cyclosporine
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Top

and to check product information (including package inserts) regarding dosage, precautions, warnings, interactions, and contraindications before administering any drug, herb, or supplement discussed herein.

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~~Art Unit or Location <1617 >~~

Telephone Number <306-3219 >

Application Number or Other Order Identifier <09/735,024 >

Author (if known) < Eritsland et al.>

Article Title <Effect of dietary supplementation... >

Journal or Book Title < American journal of cardiology>

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Volume And Issue if a Journal <vol 77 >

Year Of Publication < 1996>

Art Unit or Location <1617 >

Telephone Number <306-3219 >

Application Number or Other Order Identifier <09/735,024 >

Author (if known) < Vane et al.>

Article Title < Unknown>

Journal or Book Title <Circulation >

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Art Unit or Location <1617 >

Telephone Number <306-3219 >

Application Number or Other Order Identifier <09/735,024 >

Author (if known) <Iacoviello et al. >

Article Title <Modulation of fibrinolytic response... >

Journal or Book Title <Arteriosclerosis, thrombosis, and vascular biology >

Pages if a Journal < 1191-1197>

Volume And Issue if a Journal <bol 12 no 10 >

Year Of Publication < 1992>

Article title	Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency
Article identifier	0002914996000937
Authors	Eritsland_J Arnesen_H Gronseth_K Fjeld_N_B Abdelnoor_M
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Effect of Dietary Supplementation With n-3 Fatty Acids on Coronary Artery Bypass Graft Patency

Jan Eritsland, MD, Harald Arnesen, MD, PhD, Knut Grønseth, MD, Nils B. Fjeld, MD, and Michael Abdelnoor, MPH, PhD

Epidemiologic and experimental data suggest that a high dietary intake of long-chain polyunsaturated n-3 fatty acids may reduce the risk of atherothrombotic disease. In a randomized, controlled study, 610 patients undergoing coronary artery bypass grafting were assigned either to a fish oil group, receiving 4 g/day of fish oil concentrate, or to a control group. All patients received antithrombotic treatment, either aspirin or warfarin. Their diet and serum phospholipid fatty acid profiles were monitored. The primary end point was 1-year graft patency, which was assessed by angiography in 95% of patients. Vein graft occlusion rates per distal anastomoses were 27% in the fish oil group and 33% in the control group (odds ratio 0.77, 95% confidence interval, 0.60 to 0.99, p = 0.034). In the fish oil group, 43% of the patients had ≥1 occluded vein graft(s) compared with 51% in the control group (odds ratio 0.72, 95% confidence interval, 0.51 to 1.01, p = 0.05). Moreover, in the entire patient group, there was a significant trend to fewer patients with vein graft occlusions with increasing relative change in serum phospholipid n-3 fatty acids during the study period (p for linear trend = 0.0037). Thus, in patients undergoing coronary artery bypass grafting, dietary supplementation with n-3 fatty acids reduced the incidence of vein graft occlusion, and an inverse relation between relative change in serum phospholipid n-3 fatty acids and vein graft occlusions was observed.

(Am J Cardiol 1996;77:31–36)

An increased dietary intake of long-chain polyunsaturated n-3 fatty acids may reduce the risk of atherothrombotic disease.[1] Studies in animal models have shown that fish oil supplementation retarded experimentally induced atherosclerosis[2] and reduced intimal hyperplasia in arterialized vein grafts.[3,4] Coronary artery bypass grafting constitutes an important treatment alternative in the management of coronary artery disease. However, vein graft occlusion, mainly due to atherothrombosis, has been reported to occur in 15% to 30% of distal anastomoses during the first postoperative year and may compromise the early and long-term results of the operation.[5–8] The Shunt Occlusion Trial was a randomized, controlled study initiated to assess the effect of dietary supplementation with fish oil rich in n-3 fatty acids on 1-year graft occlusion rate in patients undergoing coronary artery bypass grafting.

METHODS

Patients: During the accrual period from May 1989 through February 1992, a total of 915 consecutive patients admitted for coronary artery bypass grafting without concomitant cardiac surgery, such as valve implantation or aneurysmectomy, were screened for participation in the study. According to protocol criteria, 305 patients were excluded. The reasons for exclusion were: medical contraindications to any of the treatment principles (n = 109), refused participation (n = 57), early (<2 days) perioperative death (n = 13) or complications (n = 32), presumed lack of compliance (n = 29), indication for anticoagulation (n = 27), and administrative reasons (n = 38). The remaining 610 patients (66.7%) were included in the study after giving their informed consent. The study was approved by the regional board of research ethics.

All patients received a bolus dose of 15 mg of warfarin on the first postoperative day. On the morning of the second postoperative day, they were randomized by random numbers in consecutively numbered sealed envelopes. A factorial 2 by 2 design was used, and patients were assigned either to a fish oil group or to a control group. Patients in each of these groups were simultaneously randomly assigned to either aspirin 300 mg once daily (Nycomed Pharma AS, Oslo, Norway) or to continue with warfarin (Nycomed Pharma AS), aimed at an anticoagulant level of 2.5 to 4.2 in terms of international normalized ratio (INR). The fish oil group received 4 capsules/day of highly concentrated ethyl esters of long-chain n-3 fatty acids (Omacor®, Pronova AS, Oslo, Norway). Each soft gelatin capsule contains 1 g of fatty acids (51% eicosapentaenoic acid C20:5n-3 and 32% docosahexaenoic acid C22:6n-3 ethyl esters) and 3.7 mg α-tocopherol as an antioxidant. Patients received verbal and written dietary advice. They were told to reduce their intake of saturated fatty acids, such as milk products, hard margarine, and meat products. Dietary records[9] were obtained from a random subsample (n = 225) before bypass surgery and repeated 1 year later. All subjects were asked to refrain from cod-liver oil and other fish oil products during the study period.

Treatment began immediately after randomization and continued throughout the first postoperative year.

From the Departments of Cardiology, Radiology, and Cardiovascular Surgery and the Research Forum, Ullevål University Hospital, Oslo, Norway. Dr. Eritsland was a research fellow of the Norwegian Council on Cardiovascular Diseases. This study was supported in part by grants from Pronova AS and Nycomed Pharma AS, Oslo, Norway. Manuscript received May 18, 1995; revised manuscript received and accepted September 18, 1995.

Address for reprints: Jan Eritsland, MD, Department of Cardiology, Ullevål University Hospital, N-0407 Oslo, Norway.

TABLE I Baseline Characteristics of 610 Patients According to Treatment Group

	Aspirin (n = 148)	Aspirin + Fish Oil (n = 143)	Warfarin (n = 145)	Warfarin + Fish Oil (n = 174)
Age (yr)	60 ± 9	61 ± 9	59 ± 9	60 ± 9
Male sex (%)	89	86	84	88
Body mass index (kg/m^2)	25.5 ± 3.0	24.9 ± 2.4	25.3 ± 2.7	25.5 ± 2.9
Smoker (%)	20	17	22	18
Diabetes (%)	11	6	6	5
Treated hypertension (%)	24	25	23	18
Previous myocardial infarction (%)	49	57	52	50
Angina class III or IV (%)*	70	74	69	68
Left ventricular ejection fraction (%)	64 ± 14	62 ± 13	65 ± 13	64 ± 14
Systolic blood pressure (mm Hg)	146 ± 23	143 ± 19	145 ± 20	144 ± 20
Diastolic blood pressure (mm Hg)	88 ± 11	87 ± 11	88 ± 11	88 ± 12

*New York Heart Association classification.
Values are expressed as mean ± SD unless otherwise noted.

TABLE II Deaths and Reasons for Deviation from Assigned Treatment

	Aspirin (n = 148)	Aspirin + Fish Oil (n = 143)	Warfarin (n = 145)	Warfarin + Fish Oil (n = 174)
Death	4	5	2	3
Deviation				
Bleeding complication	2	3	2	2
Gastrointestinal complaint	12	7	0	9
Dysphagia	0	3	0	3
Indication for anticoagulation	4	8	0	0
Contraindication to antithrombotic treatment	0	1	0	1
Nonmedical reason	2	3	3	1
Total deviations	20	25	5	16

During this period, patients were seen every 3 months. They were questioned about functional state, intercurrent diseases, bleeding episodes, and adverse effects. Major bleeding episodes were defined as bleeding necessitating operation or blood transfusion. All other bleeding episodes were classified as minor. Compliance was assessed by tablet and capsule accounts, and serum phospholipid fatty acids were determined. Prothrombin time was measured in subjects assigned to anticoagulant treatment, and intermediate measurements of prothrombin time, usually every 3 to 6 weeks, were obtained by the attending physicians.

Laboratory measurements: Blood samples after overnight fasting were obtained before, and 3, 6, and 9 months after operation. Because study treatment was discontinued 1 week before 1-year angiography, no blood samples were analyzed at 12 months. Serum total cholesterol and triglyceride levels were analyzed by enzymatic colorimetric methods using commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides, Boehringer-Mannheim GmbH, Mannheim, Germany). Serum high-density lipoprotein cholesterol was determined in the supernatant after precipitation with phosphotungstic acid and magnesium chloride.[10] Low-density lipoprotein cholesterol was calculated according to Friedewald et al.[11] The prothrombin time was measured with Thrombotest (Nycomed Pharma AS). Bleeding time was measured by the Simplate-II method (General Diagnostics, Organon Teknika, Turnhout, Belgium). Serum samples were kept frozen at −70°C until analyzed for phospholipid fatty acids. For each subject, samples obtained at different times were analyzed in a batch.

Serum lipids were extracted with n-butanol after addition of an internal standard (phosphatidyl-cholinediheptadecanoyl, Sigma, St. Louis, Missouri). An antioxidant (2,6,-di-tert.-butyl-p-kresol, Fluka AG, Buchs, Switzerland) was added to the n-butanol before extraction. Phospholipids were isolated from the total lipid extracts by solid-phase extraction on aminopropyl columns (Varian, Harbour City, California) and transmethylated. The phospholipid fatty acids were quantified by gas chromatography. FAME mixture Me-81–added C17:0 methylester (Larodan, Malmö, Sweden) was used as an external standard. A human serum pool sample was included as a control to monitor the analytic performance. The day-to-day coefficients of variation in this serum pool for C18:2n-6, C20:5n-3, and C22:6n-3 were 3.4%, 5.7%, and 5.4%, respectively (n = 58). The results were quantified as milligrams of phospholipid fatty acid per liter of serum.

Shunt angiography: One year after bypass surgery, shunt angiography was performed using a standardized procedure. Grafts were visualized by selective injection of contrast agent. A vein graft was defined as occluded when the origin of the occluded graft was visualized. If the origin was not found, an aortic root angiography was performed, and if no contrast agent was seen passing through the graft into the grafted coronary artery, the graft was defined as occluded. Similarly, if no contrast agent was seen flowing into the grafted coronary artery

from selective internal mammary artery catheterization, it was defined as occluded. All angiographies were performed and interpreted by an experienced radiologist without knowledge of the patient's assigned treatment.

Statistical analysis: The primary end point of the study was graft occlusion determined by 1-year angiography. In patients treated with either aspirin or warfarin, we assumed a vein graft occlusion rate of 20% per distal anastomoses during the first postoperative year. A sample size of 1,296 grafts was calculated to detect a 40% reduction by fish oil supplementation with a 2-sided level of significance of 0.05 and a power of 0.80. In accordance with a previous study from our institution,[12] we estimated an average of 2.7 grafts per patient, totaling 480 study patients. An increasing use of internal mammary artery grafts at the time the study was designed contributed to the decision to expand the sample size to 600 patients. Analyses were performed after the intention-to-treat principle. To adjust for interdependency between multiple vein grafts in the same patient, we also analyzed data with regard to the number of patients with ≥1 occluded vein graft(s) within each group. Finally, we compared vein graft occlusion rates in strata divided according to the relative change in concentration of serum phospholipid n-3 fatty acids during the study period. Variables on categorical data were evaluated by chi-square statistics, linear trends by Mantel-Haenszel tests,[13] and differences between other measurement variables by *t* tests. A 2-sided *p* value ≤0.05 was considered statistically significant. The EPI Info software program[14] was used. No interim analyses were performed.

TABLE III Intake of Energy and Nutrients Before and 12 Months After Bypass Operation in the Fish Oil and Control Groups

	Fish Oil (n = 124)		Control (n = 101)	
	Before	12 Months	Before	12 Months
Energy (kcal/day)*	2,202 ± 701	2,121 ± 690	2,163 ± 844	2,143 ± 699
Carbohydrate (g/day)	265 ± 88	258 ± 98	261 ± 101	266 ± 94
Protein (g/day)	92 ± 28	90 ± 29	91 ± 31	92 ± 32
Fatty acids (g/day)				
Saturated	29 ± 14	26 ± 13†	29 ± 17	27 ± 12
Monounsaturated	28 ± 12	25 ± 10†	27 ± 14	25 ± 10
Polyunsaturated*	14 ± 6	16 ± 5‡§	14 ± 8	13 ± 6
n-3 Polyunsaturated*	2.7 ± 1.3	5.5 ± 1.2‡§	2.5 ± 1.4	2.2 ± 1.0†
n-6 Polyunsaturated	10 ± 4	9 ± 4	10 ± 6	10 ± 5

*The intake of fish oil capsules is included.
†Significantly different from value before operation ($p < 0.02$ by 1-sample *t* test).
‡Significantly different from value before operation ($p < 0.001$ by 1-sample *t* test).
§Significantly different from change in the control group ($p < 0.001$ by 2-sample *t* test).
Values are expressed as mean ± SD.

TABLE IV Serum Phospholipid Fatty Acids, Serum Lipids, and Bleeding Time Before and Nine Months After Bypass Operation in the Fish Oil and Control Groups

	Fish Oil (n = 289)		Control (n = 267)	
	Before	After	Before	After
Fatty acid (mg/L)				
Linoleic (18:2n-6)	274 ± 68	259 ± 64*†	284 ± 67	321 ± 72*
Arachidonic (20:4n-6)	102 ± 29	100 ± 24†	106 ± 32	113 ± 32*
Eicosapentaenoic (20:5n-3)	38 ± 24	92 ± 31*†	33 ± 19	34 ± 23
Docosahexaenoic (22:6n-3)	113 ± 31	129 ± 27*†	112 ± 31	107 ± 32‡
Total n-3	177 ± 56	255 ± 59*†	171 ± 51	168 ± 56
Total n-6	416 ± 95	386 ± 84*†	432 ± 94	477 ± 98*
Total cholesterol (mg/dl)	256 ± 47	271 ± 49*	256 ± 48	272 ± 51*
HDL cholesterol (mg/dl)	41 ± 12	45 ± 12*	39 ± 10	41 ± 11*
LDL cholesterol (mg/dl)	180 ± 41	198 ± 45*	181 ± 44	195 ± 48*
Triglycerides (mg/dl)	175 ± 99	142 ± 89*†	183 ± 92	182 ± 110
Bleeding time (sec)	243 ± 76	282 ± 93*	249 ± 79	283 ± 84*

*Significantly different from value before operation ($p < 0.001$ by 1-sample *t* test).
†Significantly different from change in the control group ($p < 0.001$ by 2-sample *t* test).
‡Significantly different from value before operation ($p < 0.01$ by 1-sample *t* test).
Values are expressed as mean ± SD.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

RESULTS

Of 610 included patients, 317 were assigned to receive fish oil and 293 to constitute the control group. There were no significant differences between the treatment groups with respect to recorded baseline characteristics (Table I). From day 2 through the first postoperative year, 14 patients died (Table II). One patient in the warfarin group developed multiorgan failure and died from gastric bleeding in the early postoperative phase. One patient in the aspirin group died 12 days after the operation from a cerebral embolus, and 1 patient, assigned to fish oil and aspirin, died after 12 months from metastasizing prostatic carcinoma. The other 11 patients died suddenly 2 weeks to 11 months after bypass surgery. Autopsies were performed in only 3 patients.

Reasons for deviation from the assigned treatment are given in Table II. Gastrointestinal complaints causing deviation (n = 28) included dyspepsia, belching, diarrhea, and nausea. Six patients were not able to swallow the fish oil capsules. Anticoagulant treatment was required in 12 patients because of thromboembolic episodes (n = 9), persistent atrial fibrillation (2 patients), and left ventricular thrombus (n = 1). Milder abdominal complaints not resulting in withdrawal of the study medication were reported in 24 patients in the fish oil group and in 8 patients in the control group. There was no significant group difference in the total number of bleeding episodes between the aspirin and warfarin groups (23 vs 38, p = 0.10), or between the fish oil and control groups (34 vs 27, p = 0.22). However, there were more episodes of minor bleeding in patients given warfarin than in those given aspirin (35 vs 18, p = 0.036).

According to patient records, 88% of the fish oil capsules and 96% of the aspirin tablets were taken. A total of 7,722 prothrombin time measurements were recorded and the average number of measurements per patient was similar in patients given fish oil and in those given warfarin only. In the fish oil and control groups, 57%

TABLE V One-Year Graft Occlusion Rates, According to Treatment Groups

	Aspirin (n = 140)	Warfarin (n = 139)	Aspirin + Fish Oil (n = 134)	Warfarin + Fish Oil (n = 168)	Fish Oil Versus Control — Odds Ratio (95% CI)
Internal mammary artery grafts, occluded/total	13/120 (11)	16/113 (14)	13/116 (11)	25/141 (18)	1.22 (0.70–2.12)
Vein grafts, distal anastomoses, occluded/total	103/299 (34)	93/296 (31)	78/273 (29)	96/362 (27)	0.77 (0.60–0.99)*
Patients with ≥1 occluded vein graft/all patients†	66/134 (49)	71/134 (53)	57/130 (44)	69/164 (42)	0.72 (0.51–1.01)‡

*p = 0.034.
†Excluding 16 patients with internal mammary artery grafts only and 3 patients with incomplete angiography.
‡p = 0.05.
Values are expressed as number (%) unless otherwise noted.
CI = confidence interval.

and 59% of the prothrombin time measurements were within the target level of INR 2.5 to 4.2, respectively, whereas 37% and 35% of the measurements were <INR 2.5, respectively. There were no group differences in the estimated average intake of energy and nutrients before or 12 months after surgery, except for the higher intake of n-3 polyunsaturated fatty acids in the fish oil group after operation (Table III). Body weight and blood pressure were unchanged after 1 year in the fish oil as well as in the control group. The mean concentration of serum phospholipid n-3 fatty acids increased in the fish oil group, whereas the amount of n-6 fatty acids decreased in the fish oil group and increased in the control group (Table IV). The relative changes in serum phospholipid eicosapentaenoic and docosahexaenoic acids were correlated ($r = 0.76$, $p < 0.001$). In the fish oil group, serum triglyceride levels decreased by 19%, significantly different from the control group. In the fish oil and control groups, 45% and 51% of the subjects, respectively, received aspirin. The bleeding time increased moderately in both groups, and there was no group difference (Table IV).

Angiographic results: Shunt angiography was performed in 581 of the 610 included patients (95%) after a mean of 12.1 ± 1.5 months (range 4 to 19) postoperatively. Owing to persistent or new symptoms, the investigation was undertaken earlier than 11 months after bypass operation in 26 patients. Fourteen patients had died, 12 refused angiography, and in 3 patients the abdominal aorta was occluded, precluding the femoral artery approach. The procedure was incomplete in 3 additional cases due to patient reactions (n = 2) or technical failure (n = 1).

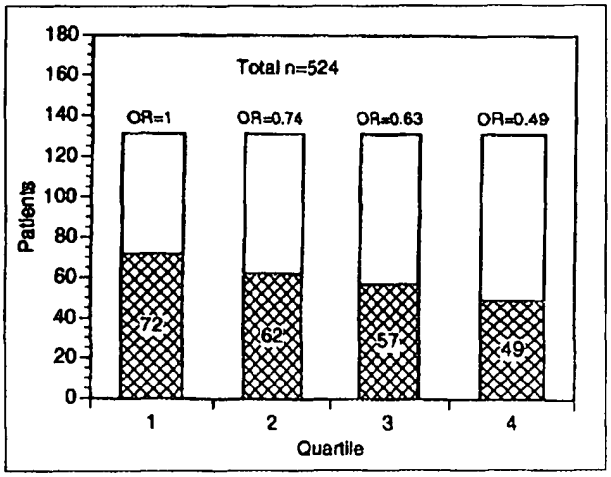

FIGURE 1. Number of patients with ≥1 vein graft occlusion *(cross-hatched areas)* in quartiles of observed change in serum phospholipid n-3 fatty acids. OR = odds ratio (p for linear trend = 0.0037).

There was no significant difference in the occlusion rates of internal mammary artery grafts between the fish oil and control groups (Table V). In patients receiving fish oil, the vein graft occlusion rate per distal anastomoses was 27% compared with 33% in the control group (odds ratio 0.77, 95% confidence interval, 0.60 to 0.99, $p = 0.034$). In the fish oil group, 43% of the patients had ≥1 vein graft(s) occluded compared with 51% of the patients in the control group (odds ratio 0.72, 95% confidence interval, 0.51 to 1.01, $p = 0.05$). Thus, an effect of fish oil supplementation on vein graft occlusions was observed in addition to aspirin as well as warfarin treatment (Table V). Between the aspirin and warfarin groups, the odds ratio for occlusion of internal mammary artery grafts was 0.64 (95% confidence interval, 0.37 to 1.12, $p = 0.10$), and the odds ratio for occlusion of vein grafts was 1.15 (95% confidence interval, 0.89 to 1.48, $p = 0.27$).

Data from shunt angiography and serum phospholipid fatty acid analyses were obtainable in 524 patients with vein grafts. Patients were divided into quartiles according to percent change in serum phospholipid n-3 fatty acids between baseline and 9 months, and the number of patients with ≥1 occluded vein graft(s) in each quartile was counted (Figure 1). There was a significant linear trend to fewer patients with vein graft occlusions, with increasing relative change in the phospholipid n-3 fatty acids (p for linear trend = 0.0037). Similar significant trends were noted when the relative changes in eicosapentaenoic ($p = 0.0048$) and docosahexaenoic ($p = 0.0037$) acids were considered.

DISCUSSION

The results indicate that an increased dietary intake of n-3 fatty acids after coronary artery bypass grafting was associated with a slightly reduced frequency of vein graft occlusions. In the randomized clinical trial, there was a lower vein graft occlusion rate in patients assigned to the fish oil group than in those assigned to the con-

trol group. Importantly, in the entire patient group, we observed an inverse relation between the relative change in serum phospholipid n-3 fatty acids during the study period and the vein graft occlusion rate. In fact, compared with patients in the lowest quartile of change in serum phospholipid n-3 fatty acids, patients in the highest quartile had an odds ratio of 0.49 (95% confidence interval, 0.29 to 0.83) for having ≥1 occluded vein graft.

We found an overall graft occlusion rate higher than expected in our patients. Most reported studies indicate 1-year vein graft occlusion rates from 15% to 30% per distal anastomoses.[5,6,15] A high inclusion rate (67%) of all eligible patients, of whom many had advanced coronary atherosclerosis, and a high percentage of angiographic end point evaluations, may have contributed to uncover these less favorable overall results. Also, in our trial, a somewhat delayed onset of antithrombotic treatment as a consequence of the randomization procedure may have resulted in an excess of very early postoperative occlusions.[5,6,15] The incidence of internal mammary artery graft occlusion also was higher than expected.[16]

An effect on vein graft patency may be due to antithrombotic as well as antiatherosclerotic properties of n-3 fatty acids.[1–4,17] It is unlikely that the effect is directly linked to an influence on serum lipoproteins, because serum cholesterol levels were not altered by fish oil supplementation, and there was no association between the reduction in serum triglycerides and vein graft patency. The effect of fish oil on vein graft patency was of equal magnitude in subjects given aspirin as in those given warfarin. Consequently, concerning the antithrombotic potential of n-3 fatty acids, effects on platelets and the coagulation system, in addition to those exerted by aspirin and warfarin, must be operative. The observed effect may largely be due to influence of n-3 fatty acids on cellular processes locally in the vessel wall. Experimental studies have shown that n-3 fatty acids may affect the function of cells involved in atherothrombosis in numerous ways. These effects include the modification of eicosanoid products in the cyclooxygenase and lipoxygenase pathways,[18–21] the reduced synthesis of cytokines and platelet-derived growth factor,[22,23] and alteration of leukocyte and endothelial cell properties.[19,24–26]

Both eicosapentaenoic and docosahexaenoic acids were supplied in mixture, and the changes in serum phospholipids of the 2 n-3 fatty acids were correlated. These changes, in turn, were both related to vein graft patency, and whether 1 of the n-3 fatty acids may be the more important in keeping the grafts patent cannot be inferred from our study.

The effect of n-3 fatty acid supplementation on the incidence of restenosis after coronary angioplasty has been addressed in several clinical studies and the results so far are equivocal.[27,28] However, it must be emphasized that the pathophysiology of coronary restenosis and vein graft occlusion differs,[7,29] and the 2 clinical conditions are not quite analogous.

Either platelet inhibition or anticoagulant treatment has been recommended after coronary artery bypass surgery.[5,6] To explore additional effects of fish oil supplementation in addition to either antithrombotic principle, we randomized for aspirin or warfarin treatment. Thus, the present study was not designed to detect differences in shunt occlusion rates between the aspirin and anticoagulation groups. However, we noted no statistical differences between these 2 groups, a conclusion supported by the results of a recently published study designed to address this issue.[30]

Generally, the fish oil supplementation was well tolerated. Adverse effects attributed to fish oil, mainly gastrointestinal complaints, were usually mild, although in some cases the supplementation had to be withdrawn (Table II). There was no statistical difference in bleeding complications between the fish oil and the control groups.

In conclusion, there was a positive association between n-3 fatty acids and vein graft patency, and the present results support the notion that an increased dietary intake of n-3 fatty acids may confer protection against atherothrombosis. This study suggests that patients undergoing coronary bypass surgery should be encouraged to keep a high dietary intake of n-3 fatty acids.

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APPENDIX

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Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study

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ABSTRACT In the National Heart, Lung and Blood Institute Type II Coronary Intervention Study, patients with Type II hyperlipoproteinemia and coronary artery disease (CAD) were placed on a low-fat, low-cholesterol diet and then were randomly allocated to receive either 6 g cholestyramine four times daily or placebo. This double-blind study evaluated the effects of cholestyramine on the progression of CAD as assessed by angiography. Diet alone reduced the low-density lipoprotein cholesterol 6% in both groups. After randomization, low-density lipoprotein cholesterol decreased another 5% in the placebo group and 26% in the cholestyramine-treated group. Coronary angiography was performed in 116 patients before and after 5 years of treatment. CAD progressed in 49% (28 of 57) of the placebo-treated patients vs 32% (19 of 59) of the cholestyramine-treated patients ($p < .05$). When only definite progression was considered, 35% (20 of 57) of the placebo-treated patients vs 25% (15 of 59) of the cholestyramine-treated patients exhibited definite progression; the difference was not statistically significant. However, when this analysis was performed with adjustment for baseline inequalities of risk factors, effect of treatment was more pronounced. Of lesions causing 50% or greater stenosis at baseline, 33% of placebo-treated and 12% of cholestyramine-treated patients manifested lesion progression ($p < .05$). Similar analyses with other end points (percent of baseline lesions that progressed, lesions that progressed to occlusion, lesions that regressed, size of lesion change, and all cardiovascular end points) all favored the cholestyramine-treated group, but were not statistically significant. Thus, although the sample size does not allow a definitive conclusion to be drawn, this study suggests that cholestyramine treatment retards the rate of progression of CAD in patients with Type II hyperlipoproteinemia.

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THE National Heart, Lung and Blood Institute Type II Coronary Intervention Study was designed to examine the hypothesis that lowering the plasma concentration of cholesterol by diet and drug therapy reduces the rate of progression of coronary artery disease (CAD). Patients with Type II hyperlipoproteinemia and CAD were randomly assigned to a low-cholesterol, low-fat diet and to receive cholestyramine treatment or they were randomly assigned to receive the same diet and placebo. Coronary lesions were assessed by coronary angiography at entry into study and after 5 years of therapy. The study protocol, recruitment strategy, and baseline findings, as well as the method for assessing angiographic change, have been previously published.[1, 2] This paper reports the results of 5 years of cholestyramine treatment on the rate of progression of CAD as measured angiographically. The relationship of plasma lipid and lipoprotein fractions to baseline coronary artery lesions and to lesion progression, and the natural history of angiographic progression, are subjects of other reports.

Methods

Study design. The study design has been described extensively elsewhere.[1] Briefly, patients were screened with two sets of eligibility criteria: elevated levels of low-density lipoprotein (LDL) cholesterol and angiographic vidence of CAD. Patients underwent coronary angiography if LDL cholesterol after 1 month of therapy with low-cholesterol, low-fat diet[3] was in the

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upper 10th percentile f the distribution of the general population *and* if they manifested presumptive evidence f CAD (previous myocardial infarction, angina, positive exercise stress test, r coronary calcification on fluoroscopy). No patient had severe incapacitating angina. Most had no symptoms or were only mildly limited on medical therapy. The only angiographic indications for exclusion from the study was the finding of more than 75% luminal narrowing of the left main coronary artery or no coronary disease meeting the criteria of 20% luminal narrowing. (Four patients, who were noted to have disease at the screening reading of the angiograms and hence were entered into the study, were later judged by the formal readings of the three panels to be free of CAD at baseline.) Patients who met the eligibility requirements and gave informed consent were continued on the diet and were randomly allocated to receive a daily dosage of 24 g cholestyramine (treatment group) or to receive placebo (control group). Dosage was adjusted in response to side effects, most of which were gastrointestinal. The study was conducted in a double-blind manner; the patient, the physician, or the panels of angiographers that evaluated the coronary angiograms did not know the treatment assignments of individual patients. In addition, lipid values and certain other chemistries obtained during the follow-up that might provide clues as to type of treatment were not released to patients or personnel involved with patient care. Patients came to the Clinical Center at the National Institutes of Health in Bethesda for monthly visits at which time cardiac status, diet, and drug adherence and side effects were monitored. Plasma cholesterol and triglycerides were determined every 2 months and LDL cholesterol and high-density lipoprotein (HDL) cholesterol were measured semiannually. The methods used for analyses of plasma lipids and lipoproteins have been previously published.[1] At the end of 5 years of follow-up, each patient was hospitalized and a repeat coronary angiogram was performed.

In the planning phase, calculations of sample size indicated a desired study population of 250 patients. However, the entry criteria were rigorous and only 143 patients could be recruited during the 54 month recruitment period of the study. Of these 143 patients, there were 116 who had a repeat angiogram and hence, a determination of CAD progression. Since the weight of laboratory and epidemiologic evidence suggested that reduction of lipid concentrations would retard CAD progression, the study was designed to look for benefit only. Thus, power for the statistical test of the results was calculated for a one-tailed significance test of level .05. If the proportion of the control group that demonstrated CAD progression was .60, then with 116 patients the study had a 71% chance to detect in the treatment group a relative reduction of 33% in the rate of CAD progression.

During the 5 year follow-up of the study there were 12 deaths (table 1). In addition, 10 patients withdrew from the study, and there were five patients wh c ntinued t follow their prescribed treatment regimen and attended the clinic but did not consent to angiography at 5 years. Thus, of the 143 patients who entered the study, there were 116 wh had angi grams performed both initially and after 5 years f follow-up. Table 1 enumerates the f ll w-up status by treatment assignment. The initial protocol required a follow-up coronary angiogram after 2 years of therapy.[1] Evaluation of the first 31 patients revealed change in CAD as measured by angiography in only nine patients. Because the number of patients exhibiting progression of disease at 2 years was lower than expected, the protocol was changed to perform follow-up angiography only after 5 years of therapy.

Baseline characteristics of the entire study population of 143 have been presented elsewhere.[1] Tables 2, 3, and 4 present baseline characteristics of the 116 patients who had a final angiogram. In a comparison of treatment groups, the cholestyramine group had significantly higher systolic blood pressure, higher baseline triglycerides, more patients with abnormal ventricular contractile function, and fewer patients who consumed 10 or more alcoholic drinks per week; in the analysis of effect of treatment these variables were used as covariates for adjustment. To assess whether or not the 116 patients who underwent follow-up angiography after 5 years (and hence a determination of disease progression) are representative of the 143 who entered the study, we compared the characteristics of the 116 patients with those of 27 patients who did not undergo a follow-up angiogram after 5 years. The 27 patients include 12 who died, 10 lost to follow-up, and five who refused to undergo a final angiogram. The 116 did not differ significantly from the 27 in baseline characteristics; nor did the baseline characteristics of the 27 differ substantially among the deaths, dropouts, and refusals.

Measures of lipid response. For each patient, lipid values were summarized by a prediet baseline mean, a postdiet baseline mean (measurements after diet therapy was begun but before drug therapy), and annual means. A 5 year follow-up average was calculated as the mean of the five yearly means. The percent change was calculated as the change from baseline postdiet mean to the 5 year follow-up average.

Outcome determination. To establish the precision and accuracy of angiographic readings of both cine and cut films by expert angiographers, an experiment for reading angiograms was conducted. This demonstrated that agreement by at least two out of three independent review panels regarding the occurrence of change in a segment of the arterial tree was required to establish a reliable measure of such change.[2] The procedure for reading the baseline and 5 year follow-up angiograms based on the results of the experiment has been reported.[1] In summary, the baseline and 5 year follow-up angiograms were evaluated as a pair, with the temporal sequence of the films and the treatment assignment unknown to the readers. The evaluation was per-

TABLE 1
Follow-up status by treatment

	Placebo		Cholestyramine		Total	
	No. of patients	%	No. of patients	%	No. of patients	%
No sequential angiography						
Died	7	9.7	5	7.0	12	8.4
Withdrawn before completion	5	6.9	5	7.0	10	7.0
Completed but no final angiogram	3	4.2	2	2.8	5	3.5
Sequential angiography	57	79.2	59	83.1	116	81.1
Total	72	100.0	71	100.0	143	100.0

TABLE 2
Baseline characteristics by treatment

	Placebo (n = 57)		Cholestyramine (n = 59)		Total (n = 116)	
	No. of patients	%	No. of patients	%	No. of patients	%
History						
Age (yr)						
21–35	3	5.3	7	11.9	10	8.6
36–45	17	29.8	20	33.9	37	31.9
46–55	37	64.9	32	54.2	69	59.5
mean ± SE	46.9 ± 0.82		45.4 ± 0.92		46.1 ± 0.62	
Sex						
Male	46	80.7	48	81.4	94	81.0
Smoking history						
Never smoked	9	15.8	12	20.3	21	18.1
Formerly smoked	27	47.4	24	40.7	51	43.0
Presently smoke	21	36.8	23	39.0	44	37.9
Mean no. cigarettes/day ± SE	27.6 ± 2.7		23.0 ± 1.9		25.3 ± 1.7	
Alcohol[A]						
10 or more drinks/week	24	42.1	14	23.7	38	32.8
Overall physical activity compared with others						
More active	16	28.1	10	16.9	26	22.4
Same	29	50.9	31	52.5	60	51.7
Less active	12	21.1	18	30.5	30	25.9
Prior myocardial infarction	11	19.3	16	27.1	27	23.3
Current chest pain	15	26.3	23	39.0	38	32.8
Symptomatic						
Yes (MI and/or angina)	25	43.9	33	55.9	58	50.0
NYHA classification						
I	51	89.5	45	76.3	96	82.8
Systolic blood pressure[B]						
mean ± SE	118.6 ± 1.7		125.8 ± 1.4		122.3 ± 1.1	
Diastolic blood pressure						
mean ± SE	78.5 ± 1.2		79.6 ± 1.2		79.1 ± 0.85	
Xanthoma present	26	45.6	28	47.5	54	46.6
Arcus present	37	64.9	32	54.2	69	59.5

NYHA = New York Heart Association; MI = myocardial infarction.
[A] $p < .05$ for difference between placebo and cholestyramine.
[B] $p < .01$ for difference between placebo and cholestyramine.

formed by three separate panels, each consisting of three experts. Angiographers on each panel reached a consensus evaluation.

Data were recorded on forms modified from the Coronary Artery Surgery Study (CASS).[4] This required the evaluation of each of 27 coronary artery segments for the presence and extent f a lesion. The use of calipers to assist in this task was encouraged. The 27 arterial segments defined by CASS standards were classified for this study according to size and location as major, intermediate, or minor. The segments contained in each category differ according to dominance of the individual's coronary artery system. The segments included in each category are given in Appendix A.*

Segments were also classified as normal or as exhibiting one or multiple lesions. Appendix B (see footnote) provides the number of normal segments and the number of lesions of each size by location as identified by each panel. Because of anatomic and pathologic variation in the individual coronary arteries, few patients had all 27 segments imaged and evaluated. Also, for some patients some segments had more than one lesion. These circumstances made it impossible to obtain a denominator uniform for all patients. Among the 116 participants, the panels recorded an average of 431 lesions producing less than 50% luminal diameter reduction, 88 lesions causing 50% to 69% narrowing, 110 lesions causing 70% to 99% narrowing, and 48 total occlusions. Since the distribution of lesions was similar in the two treatment groups, only the totals are presented here.

Panels recorded the change, if any, in luminal diameter for each lesion on the two sets of films and also indicated whether this was a probable or definite change. Since the temporal sequence of the sets of films was not specified, the panels could not determine progression or regression but only change. The

*See National Auxiliary Publications Service document No. 04143 for pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance U.S. funds only, $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada add postage of $4.50 for the first 20 pages and $1.00 for each additional page; $1.50 for microfiche postage.

TABLE 3

Lipid baseline characteristics by treatment (mg/100 ml, mean ± SE)

	Placebo (n = 57)	Cholestyramine (n = 59)	Total (n = 116)
Prediet lipids[A]			
Plasma cholesterol	315.2 ± 5.7	331.4 ± 6.4	323.4 ± 4.4
Triglyceride	154.7 ± 6.8	173.3 ± 8.4	164.2 ± 5.5
HDL	40.1 ± 1.5	38.2 ± 1.3	39.1 ± 1.0
LDL	244.2 ± 5.6	258.5 ± 6.4	251.5 ± 4.3
Postdiet lipids[B]			
Plasma cholesterol	293.1 ± 6.4	309.6 ± 7.1	301.5 ± 4.8
Triglyceride[C]	131.2 ± 5.4	155.8 ± 8.0	143.7 ± 5.0
HDL	38.7 ± 1.3	37.7 ± 1.2	38.2 ± 0.9
LDL	229.4 ± 6.1	242.4 ± 7.3	236.0 ± 4.8

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[A]Mean of visits 2 and 3.

[B]Mean of visits 4, 5, and 6 for plasma cholesterol and triglyceride, 4 and 6 for HDL, LDL.

[C]$p < .05$ for difference between placebo and cholestyramine group.

designation of progression or regression was added in the analysis phase.

A lesion change placed in one segment by one panel may be placed in a different, although nearby, segment by other panels. Therefore, to ensure that comparison of readings among the panels involved observations of the *same* lesion change, lesions were aligned. Among the panels the alignment of the changed lesions was carried out according to the following: If there were three different locations in contiguous segments for the changed lesion, it was aligned to the middle segment. If there were two different locations (in close but not anatomically contiguous segments) for the changed lesions from the three panels, then the changed lesion was aligned to the segment recorded by the two agreeing panels. If there were two different locations in anatomically contiguous segments for a lesion itemized as changed by only two of the three panels, the changed lesion was aligned to the distal segment. This procedure was carried out independently by two investigators. Disagreements were to be resolved by the Steering Committee, but that occasion did not arise.

Confirmed lesion changes. Once lesion changes observed by individual panels were aligned, a determination of change was based upon a two of three panel majority. By definition, a confirmed change required at least two or three of the panels to agree that a change occurred. Such changes were classified as shown in table 5.

The first method of analysis focused on lesions. Since each lesion would be exposed to the same blood lipid levels, several lesions in one patient were not assumed to change independently and so the patient was considered as the primary unit of analysis. Once a definition of lesion change was established we adopted the following definition of change for a patient:

Definite progression — At least one lesion with definite progression and no lesion with regression.

Probable progression — At least one lesion with probable progression and no lesion with regression or definite progressi n.

Probable regressi n — At least one lesion with probable regressi n and n lesi ns with definite regression or any progressi n.

Definite regressi n — At least ne lesion with definite regression and no progression.

Mixed response — regressi n and progression: lesi n progression and lesion regression in the same patient, whether definite or probable. Patients with mixed response were further classified as having both definite regression, both probable progression and probable regression, or definite progression with probable regression.

No change — No lesion observed as changed by at least two panels.

Once patients were classified according to the above scheme, four dichotomous end points for progression or no progressi n were defined. The four different measures of outcome that reflect different degrees of certainty of progression of CAD of patients were defined: (1) definite lesion progression and no lesion regression, (2) definite lesion progression with or without lesion regression, (3) definite or probable lesion progressi n and no lesion regression, and (4) definite or probable lesi n progression with or without lesion regression. For each of these measures of outcome, patients were cross-classified by treatment group and outcome; chi-square statistics were calculated for the resulting two-by-two tables to test effect of treatment on progression of disease.

In addition to the overall qualitative classification of change, we considered other important quantitative measures of angiographic change based on the number and severity of lesions that change. Appendix C (see footnote p. 315) provides definitions of quantitative change as well as methodology for calculation of standard errors and statistical hypothesis tests for quantitative measures of change.[5]

Methods of multivariate analysis. Crude effects of treatment for each of the four measures of outcome of CAD were adjusted with multivariate logistic regression models to ensure that the results were not confounded by unequal distribution of risk factors between the two treatment groups.[6] In this analysis the outcome variable was CAD progression and the variables used to adjust treatment effect were those that were out of balance at baseline ($p < .05$). Z scores are reported for treatment and for each of the baseline variables. The Z scores, which are the regression coefficients divided by their standard errors, have approximately a standard normal distribution. A positive Z score represents a positive association with CAD progression, and a negative score represents a negative association. The critical values for a one-sided test, alpha = .05, are ±1.64.

Statistical computing. Statistical Package for the Social Sciences (SPSS) programs were used for descriptive statistics. Biomedical Computer Programs P-series (BMDP) were used for logistic regression analysis. Computer storage and retrieval of data were accomplished through use of the 1022 Database Management System. The algorithms for angiographic measures of change were written specifically for this study. At the conclusion of the study, displays were designed to present lipid values and angiographic results for each individual patient. Examples are given in Appendix D (see footnote p. 315). The definitions for angiographic change and the algorithm for alignment described above are illustrated in this Appendix as well.

Quality control of panels studying angiograms. To assess reader reproducibility, 18 pairs of angiograms (baseline and follow-up) selected at random were evaluated by each of the three panels a second time, at least 6 months after the first evaluation. The sample was enriched with films that exhibited confirmed lesion changes. The panels were not told that these films, which were interspersed among new pairs, had been shown previously. Assessment f 14 f the pairs was the same n the first and second reading (six no change, one mixed response, one probable progression, and six definite progression). Three pairs that were judged as showing probable progressi ns and one judged as sh wing probable regressi n n the first reading were classified as exhibiting no change on the

TABLE 4
Angiographic and ventriculographic baseline characteristics

	Placebo (n = 57)		Cholestyramine (n = 59)		Total (n = 116)	
	No. of patients	%	No. of patients	%	No. of patients	%
Number of major vessels with 50% or more luminal diameter reduction						
0	22	38.6	22	37.3	44	37.9
1	17	29.8	15	25.4	32	27.6
2	10	17.5	16	27.1	26	22.4
3	4	7.0	5	8.5	9	7.8
Left main artery disease	4	7.0	1	1.7	5	4.3
Dominance						
Left	4	7.0	2	3.4	6	5.2
Location of disease						
Right artery	29	50.9	32	54.2	61	52.6
Left anterior descending artery	26	45.6	25	42.4	51	44.0
Left circumflex artery	21	36.8	18	30.5	39	33.6
Number of lesions						
0[A]	1	1.8	3	5.1	4	3.4
1–3	12	21.1	15	25.4	27	23.3
4–6	18	31.6	16	27.1	34	29.3
7–9	17	29.8	17	28.8	34	29.3
10 or more	9	15.8	8	13.6	17	14.7
Number of lesions 50% or more						
0	15	26.3	18	30.5	33	28.4
1	12	21.1	10	16.9	22	19.0
2	8	14.0	7	11.9	15	12.9
3	10	17.5	13	22.0	23	19.8
4 or more	12	21.1	11	18.6	23	19.8
Regional contractile function abnormal[B,D]	10	17.5	21	35.6	31	26.7
Ejection fraction 55% or less	19	33.3	15	25.4	34	29.3
LV end-diastolic pressure 14 mm Hg	12	21.1	15	25.4	27	23.3
Left ventricular function abnormal[C]	20	35.1	28	47.5	48	41.4

[A]At screening reading of angiogram, disease was noted although formal three panel readings did not observe any disease.
[B]Regional contractile function is defined as normal if focal akinesis, hypokinesis, and dyskinesis are all absent.
[C]Abnormal left ventricular function is defined as at least one of the following: ejection fraction ≤55%, left ventricular end-diastolic pressure >14 mm Hg or regional contractile function abnormal.
[D]$p < .05$ for difference between placebo and cholestyramine.

second reading. This appropriately suggests that a determination of definite change is highly reproducible and probable change is less so. Of the eight angiographic pairs that were classified as changed on both primary and second readings, the number of lesion changes was the same for four patients, was greater on the primary reading for two patients, and was greater on the second reading for two patients. For presentation of final results only the first readings were used, although the results would be essentially the same if the second readings were used.

Results

Lipid response. A high level of adherence was achieved by the study patients throughout the trial. At least 90% adherence to drug dosage of 24 g daily (as determined by packet count) was achieved by 73.7% of the placebo-treated patients and 79.7% of the cholestyramine group (not statistically significantly different).

The observed lipid response of the 116 final study patients by treatment is summarized in table 6. When these lipid responses are considered as percent change from the baseline after diet but before drug therapy, the following results are noted: the cholestyramine-treated group achieved a 26% reduction in LDL cholesterol and the placebo group achieved a 5% reduction, both averaged over the 5 year period f foll w-up, indicating a statistically significant ($p < .001$) effect f drug treatment on LDL cholesterol. Similar differences are seen for total plasma cholesterol (17% vs 1% decrease). HDL cholesterol increased in both treatment

TABLE 5
Definitions of confirmed coronary segment change based on three panel readings

Consensus on change	Possible panel combinations
Confirmed definite	def, def, def
	def, def, prob
	def, def, 0
Confirmed probable	def, prob, prob
	prob, prob, prob
	def, prob, 0
	prob, prob, 0
Confirmed no change	def, 0, 0
	prob, 0, 0
	0, 0, 0

def = definite change (i.e. clearcut difference, no question in our minds); prob = probable change (i.e. we feel there is a difference but it was a close decision); 0 = no change or indeterminate.

groups: 2% in placebo and 8% in the cholestyramine group. Although triglycerides were significantly higher in the cholestyramine group than in the placebo group at each annual follow-up, triglycerides were higher in the cholestyramine group at baseline as well. Hence, the increases in triglyceride levels over time are not significantly different in the placebo (26%) and cholestyramine (28%) groups. Details of the lipid response over time are presented in the companion report (p. 325, ref. 27).

TABLE 6
Five year lipid changes

	Total cholesterol	LDL_c	HDL_c	Triglyceride
Placebo (n = 57)				
Postdiet baseline (mg/100 ml)	293	229	39	131
5 year mean (mg/100 ml)	289	219	39	161
Difference (mg/100 ml)	−4	−10	0	30
p value for difference[A]	NS	<.001	NS	<.001
Mean percent change[B]	−1	−5	2	26
Cholestyramine (n = 59)				
Postdiet baseline (mg/100 ml)	310	242	38	156
5 year mean (mg/100 ml)	256	178	41	193
Difference (mg/100 ml)	−54	−64	3	37
p value for difference[A]	<.001	<.001	<.001	<.001
Mean percent change[B]	−17	−26	8	28
Treatment comparison				
p value for difference in percent change between placebo and cholestyramine[C]	<.001	<.001	NS	NS

LDL_c = low-density lipoprotein cholesterol; HDL_c = high-density lipoprotein cholesterol.

[A]Paired t test (two-sided).

[B]Percent change was computed for each individual and then a mean was calculated. This result can differ from the percent change of the mean group values.

[C]t test for independent samples.

Safety monitoring. Clinical chemistry and laboratory values were monitored for evidence of drug toxicity during the course of the 5 year follow-up. Those values not differing between the placebo and cholestyramine groups at baseline and not subsequently changing included vitamin A, serum iron, hemoglobin, hematocrit, SGOT, sodium, chloride, carbon dioxide, phosphorus, calcium, potassium, and thyroxin.

Figure 1 displays the mean values over time for each treatment group for those items that did show a difference between treatment groups. Alkaline phosphatase and total iron-binding capacity rose and carotene values dropped in the cholestyramine group.

Side effects were evaluated through the use of a printed list answered by the patient. Each item had a choice of responses that were none, slight, moderate, and severe. Table 7 contains the incidence of moderate

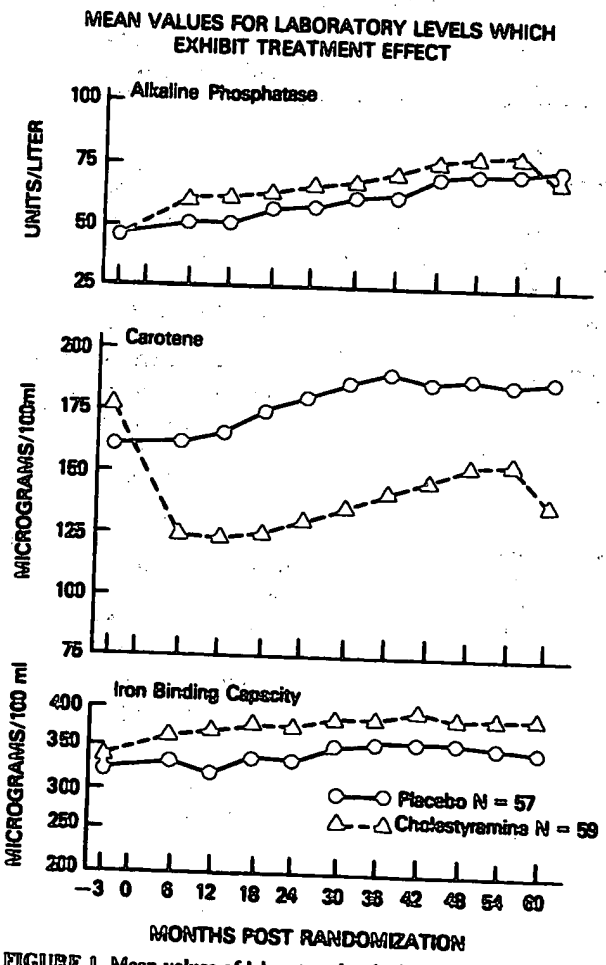

FIGURE 1. Mean values of laboratory levels that exhibited treatment effect.

TABLE 7
Incidence of moderate and severe side effects by treatment

	Baseline				Baseline				First year				5 years			
	Placebo (n = 72)		Cholestyramine (prediet-predrug) (n = 71)		Placebo (n = 72)		Cholestyramine (postdiet-(predrug) (n = 71)		Placebo (n = 70)		Cholestyramine (n = 68)		Placebo (n = 57)		Cholestyramine (n = 69)	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Gastrointestinal																
Belching/bloating	8	11.1	9	12.7	0	0.0	5	7.0	1	1.4	3	4.4	3	5.3	3	5.1
Constipation	1	1.4	2	2.8	1	1.4	1	1.4	0	0.0	1	1.5	2	3.5	3	5.1
Gas	15	20.8	11	15.5	3	4.2	5	7.0	2	2.9	5	7.4	4	7.0	3	5.1
Heartburn	12	16.7	10	14.1	0	0.0	2	2.8	0	0.0	1	1.5	0	0.0	3	5.1
Other																
Abdominal pain	3	4.2	5	7.0	0	0.0	2	2.8	0	0.0	1	1.5	0	0.0	2	3.4
Drowsiness	4	5.6	8	11.3	2	2.8	2	2.8	0	0.0	2	2.9	1	1.8	5	8.5
Itching	7	9.7	5	7.0	2	2.8	3	4.2	1	1.4	1	1.5	0	0.0	1	1.7
Leg cramps	6	8.3	9	12.7	1	1.4	3	4.2	2	2.9	4	5.9	1	1.8	5	8.5
Nervousness	16	22.2	18	25.4	2	2.8	10	14.1^	1	1.4	3	4.4	3	5.3	5	8.5
Rash	3	4.2	3	4.2	2	2.8	3	4.2	0	0.0	1	1.5	0	0.0	1	1.7
Weakness	5	6.9	3	4.2	0	0.0	2	2.8	0	0.0	1	1.5	0	0.0	3	5.1

^p < .05 for difference between placebo and cholestyramine.

or severe side effects by treatment at (1) baseline before diet and before therapy, (2) after diet and before therapy, (3) 1 year follow-up, and (4) 5 year follow-up. No increase in side effects occurred during follow-up. In fact, the highest incidence of side effects occurred before diet and drug therapy. The only statistically significant difference between placebo and cholestyramine for any side effect at any of these four study times occurred after diet but before drug therapy. At that point there were more cholestyramine-treated patients who reported nervousness.

Risk factors were monitored during follow-up. There was no significant change in blood pressure or weight for either treatment group. Smoking habits remained the same for most patients, although two of the placebo-treated patients and four of the cholestyramine-treated patients who smoked at baseline were not smoking at 5 year follow-up, and six of the placebo-treated patients and two of the cholestyramine-treated patients who were former smokers at baseline had resumed smoking again at 5 years.

Angiographic changes. Each patient was classified by change in CAD according to the qualitative categories

TABLE 8
CAD changes in patients by treatment

	Placebo (n = 57)		Cholestyramine (n = 59)		Total (n = 116)	
	No. of patients	%	No. of patients	%	No. of patients	%
Definite progression	20	35.1	15	25.4	35	30.2
Probable progression	8	14.0	4	6.8	12	10.3
Mixed response	1	1.8	5	8.5	6	5.2
No change	24	42.1	31	52.5	55	47.4
Probable regression	3	5.3	2	3.4	5	4.3
Definite regression	1	1.8	2	3.4	3	2.6

TABLE 9
CAD changes in patients: analyses by treatment

	Placebo (n = 57)		Cholestyramine (n = 59)		Total (n = 116)	
	No. of patients	%	No. of patients	%	No. of patients	%
Definite progression with no regression	20	35.1	15	25.4	35	30.2
Definite progression with or without regression	21	36.8	19	32.2	40	34.5
Definite or probable progression with no regression^	28	49.1	19	32.2	47	40.5
Definite or probable progression with or without regression	29	50.9	24	40.7	53	45.7

^p = .03 of the difference between placebo and cholestyramine.

TABLE 10

CAD changes in patients with lesions producing 50% or more luminal diameter reduction (n = 83 patients with at least one lesion ≥ 50% at baseline)[A]

	Placebo (n = 42)		Cholestyramine (n = 41)		Total (n = 83)	
	No. of patients	%	No. of patients	%	No. of patients	%
Definite progression	9	21.4	4	9.8	13	15.7
Probable progression	5	11.9	1	2.4	6	7.2
Progression[B] (definite or probable)	14	33.3	5	12.2	19	22.9
Mixed response	0	0.0	0	0.0	0	0.0
No change	24	57.1	31	75.6	55	66.3
Probable regression	2	4.8	2	4.9	4	4.8
Definite regression	2	4.8	3	7.3	5	6.0
Regression (definite or probable)	4	9.6	5	12.2	9	10.8

[A]Although patients included in this table are a subgroup of those included in table 8, there are more patients classified as having regression. This occurs since a patient with a lesion less than 50% that progresses and with a lesion more than 50% that regresses is classified as mixed response on table 8 and as regression here.

[B]p = .02 for one-sided test.

of definite progression, probable progression, definite regression, probable regression, no change, or mixed response. Table 8 displays the results of this patient classification for the two treatment groups. Patients were then divided into two groups, either CAD progression or no progression, according to each of the four cut points for defining progression. The results are shown in table 9. First, we examined the results of progression without regression. Definite progression was identified in 35.1% of the placebo group and in 25.4% of the cholestyramine group. This difference was not statistically significant at the .05 level. When the definite and probable progression categories were combined, progression of the coronary lesions occurred in 49.1% of the placebo group but in only 32.2% of the cholestyramine group, a result that was significant at p = .03 for a one-sided hypothesis test.

Whether the category of patients who exhibit both progression and regression of lesions represents deterioration is unclear, particularly since within the category there are different degrees of change. Among the five patients with mixed response in the cholestyramine group, one exhibited definite progression with definite regression, one exhibited probable progression with probable regression, and three exhibited definite progression with probable regression. The placebo-treated patient with mixed response had both definite progression and definite regression.

If we include patients with mixed response and reclassify patients on the basis of lesion progression whether or not lesion regression is present, definite CAD progression occurs in 36.8% of the placebo group and in 32.2% of the cholestyramine group. When probable progression is combined with definite progression, the extent of CAD progression is 50.9% of the placebo group vs 40.7% of the cholestyramine group. The trend, suggesting a treatment benefit of cholestyramine, is not statistically significant at the .05 level.

Further differential effects of treatment were examined by considering only those lesions that produced 50% or more reduction in luminal diameter at baseline. Of the 116 patients, there were 83 who had at least one lesion equal to or greater than 50% at baseline study. The results considering only these patients and lesions are presented in table 10. No patients in this subgroup had a mixed response. The percentage of patients who exhibited definite progression was 21.4% in the placebo group and 9.8% in the cholestyramine group, a result not statistically significant. If probable progression is combined with definite progression, then 33.3% of the placebo group and 12.2% of the cholestyramine group have progression of disease, a difference favoring cholestyramine at p = .02.

Table 11 presents a comparison of the proportion of lesions per patient (see Appendix C [see footnote p. 315] for definition and methodology) that changed. When all lesions that progressed are considered, an average of 12.1% of baseline lesions in the placebo group progressed; this value is similar to that found in the cholestyramine group (10.9%). When progressions of lesions with 50% or greater stenosis are considered, the average proportion that progressed in the placebo group, 14.3%, is significantly greater than the 5.4% progression rate observed in the cholestyramine group (p < .05). The placebo group also had a greater proportion of lesions that progressed to total occlusion. When only those lesion progressions judged to be definite are considered, similar differences in the comparisons between placebo and cholestyramine are seen, although none of the differences is statistically significant. The patients in the placebo group exhibit an average of 1.4% of lesions regressed compared with 3.1% of the lesions regressed in the cholestyramine group. In addition, more segments in the placebo group than in the cholestyramine group that were judged to be normal at baseline study developed new lesions. All of the comparisons presented in table 11 favor benefit in the cholestyramine-treated group, although the criteria are not independent and only one difference (progression

TABLE 11

CAD changes in patients: comparison of ratios by treatment[A]

Ratios	Placebo (n = 57)			Cholestyramine (n = 59)			
	No. of lesions[B]	Ratio[C]	SE(R)	No. of lesions[B]	Ratio[C]	SE(R)	Z value[D]
Progressed lesions[E,F] / Initial lesions	347	0.121	0.027	322	0.109	0.025	.33
Progressed lesions[F] / Initial lesions ≥50%	126	0.143	0.030	112	0.054	0.022	2.43[H]
Progressions to 100%[E,F] / Initial lesions	347	0.038	0.011	322	0.012	0.006	1.92
Definite progressed lesions[E] / Initial lesions	347	0.087	0.023	322	0.084	0.021	.08
Definite progressed lesions / Initial lesions ≥50%	126	0.087	0.024	112	0.045	0.020	1.37
Definite progressions to 100%[E] / Initial lesions	347	0.035	0.011	322	0.012	0.006	1.73
Regressed lesions[G] / Initial lesions	347	0.014	0.006	322	0.031	0.010	−1.43
New lesions / Normal segments	771	0.021	0.006	823	0.015	0.005	.79
New lesions ≥50% / Normal segments	771	0.014	0.006	823	0.007	0.004	.96
Lesions <50% to >50% / Initial lesions <50%	221	0.018	0.007	210	0.010	0.004	1.01

SE = standard error; R = ratio.

[A]The discrepancy in total numbers of lesions given by this table and Appendix B (see footnote p. 315) is due to rounding error. For Appendix B the total number of lesions for all patients is tabulated for each panel then a mean is taken. For this table the total number of lesions for each patient is tabulated for each panel. A three-panel mean for each patient is calculated and rounded to the nearest integer.

[B]Denominator number of lesions.

[C]Numerator can be calculated as number of lesions times ratio.

[D]For determination of Z value see Appendix C (see footnote p. 315).

[E]New lesions were excluded from the numerator.

[F]Definite and probable progressions are included.

[G]Definite and probable regressions are included.

[H]$p < .05$ for difference between placebo and cholestyramine.

of lesions with 50% or greater stenosis) reaches statistical significance. The comparisons in table 11 were also calculated for various subgroups of lesions: lesions in the right coronary artery, lesions in the left main artery, lesions in the left anterior descending artery, lesions in the left circumflex artery, lesions in major locations, lesions in intermediate locations, and lesions in minor locations. Similar trends in favor of the cholestyramine-treated group were observed, but sample sizes were too small to drawn meaningful conclusions.

Adjusted effects of treatment. Among the baseline characteristics f the 116 patients there were significant ($p < .05$) differences between the placebo and cholestyramine groups for the foll wing: alcohol consumption, ventricular regional contractile function, systolic blood pressure, and postdiet triglyceride levels. A logistic regression model was used to adjust for these imbalances to provide a more exact description of effect of treatment.

In the logistic model the outcome is dichotomous. The model was fit with the four different definitions for CAD progression. As described above the first was definite progression with no regression. The second was definite progression with r without regression, the third was progressi n with no regression, and the fourth was progression with or without regressi n. Table 12 first gives Z scores for the effect of crude treatment. Next, Z scores are given for treatment adjusted for the four baseline variables described above as well

TABLE 12
Multivariate logistic regression analysis: Z scores

	End points			
	Definite progression No regression	Definite progression with/without regression	Definite or probable progression No regression	Definite or probable progression with/without regression
Model 1 (crude treatment effect)				
Cholestyramine treatment	−1.13	−.05	−1.85^	−1.10
Model 2 (treatment adjusted by baseline imbalances $p < .05$)				
Cholestyramine treatment	−1.82^	−1.63	−2.42^B^	−2.07^
Systolic blood pressure (mm Hg)	1.41	2.08	1.84	2.68
Triglycerides (mg/100 ml)	−.48	.49	−1.11	−.41
Alcohol (>10 drinks per week)	−.14	−.52	.13	.05
Regional contractile function abnormal	2.39	1.84	2.46	1.87

^$p < .05$.
^B^$p < .01$.

as the Z scores for the other variables. Triglycerides and alcohol were not related to outcome. Abnormal contractile function and high systolic blood pressure were both more prevalent in the cholestyramine group and were both associated with progression. Thus, when adjustment was made for these variables, a more pronounced effect of treatment was obtained. The adjusted Z score for the end point definite progression with no regression is −1.82, indicating a significant effect of treatment. The Z score for the end point definite progression with or without regression is −1.63, which just approaches significance at the .05 level. For the two end points that include probable progression, the effect of treatment is significant since the Z scores are −2.46 and −2.07.

Multiple end points. Seven patients died and five had a nonfatal myocardial infarction (three of which were documented) in the placebo group, whereas five died and three had a nonfatal myocardial infarction (one of which was documented) among patients in the cholestyramine group. Seven of the eight patients with nonfatal myocardial infarction had a final angiogram. Of these seven, six were noted to have progression as determined angiographically. Death, myocardial infarction, progression, or both myocardial infarction and angiographic progression occurred in 29 cholestyramine-treated patients and in 37 placebo-treated patients. The odds that a cholestyramine-treated patient died, had a myocardial infarction, or had progression in relation to the odds that a placebo-treated patient died, had a myocardial infarction, or had progression is 0.60. A 95% confidence interval for the odds ratio is 0.30 to 1.21. An odds ratio of 1.0 indicates equal odds for the undesirable outcomes. Since the 95% confidence interval includes 1.0 we can not reject the null hypothesis that the groups are the same at the alpha .05 level.

Discussion

Plasma concentrations of cholesterol and LDL cholesterol are directly related to the prevalence and incidence of CAD.[7-11] However, although lowering the plasma concentrations of cholesterol in nonhuman primates with diet-induced hypercholesterolemia will delay the progression and actually lead to regression of existing atherosclerotic plaques,[12-16] similar effects of lowering cholesterol levels on coronary atherosclerosis have not yet been clearly shown to occur in man.[10, 17, 18]

The ultimate test of a clinical hypothesis dealing with therapeutics is the double-blind, randomized, placebo-controlled clinical trial. Several primary and secondary prevention clinical trials that use diet alone[15, 17, 19, 20] and diet plus drugs[17, 18, 21] have been published. None of the trials has reported conclusive results.[10, 15, 17, 20] All the trials to date have depended on detecting differences in the clinical end points of death and heart attack to demonstrate an effect of treatment. This has necessitated long periods of follow-up and large numbers of participants. In trials that have relied on diet alone, a cholesterol differential between control and treatment groups of only about 10% and problems with patient dropouts have weakened their statistical power.[15, 17, 18] When drugs have been added to diet to enhance the degree of cholesterol lowering, problems related in part to the metabolic effects of the drugs have

interfered with the interpretation of the results of the trials.[20, 22-25]

In this study we attempted to overcome most of these problems by our choice of drug and end point. Cholestyramine, a nonabsorbed bile acid sequestering resin, was used to enhance the effects of a low-cholesterol diet. Cholestyramine has previously been shown to reduce concentrations of LDL cholesterol; it is also a drug that has no consistent physiologic effects that would compromise its use in a double-blind protocol.[21, 26] In addition, in nonhuman primates cholestyramine has been shown to result in the regression of atherosclerotic coronary lesions in animals with both spontaneous and diet-induced hypercholesterolemia.[16] In this double-blind study in which the treatment group received cholestyramine and diet while the control group received placebo and diet, a treatment-controlled difference in LDL cholesterol of more than 20% was achieved. Since a more specific end point with a reasonably high-event rate, that is, change in the degree of coronary artery narrowing (as determined by serial coronary angiograms) was used, many fewer patients were required than in studies using clinical end points with a low-event rate. The major limitation of our study derived from our inability to recruit the 250 subjects with Type II hyperlipoproteinemia and CAD that was projected for the statistical success of this trial.

Analysis of the data indicated that while no definitive evidence emerged indicating that therapy caused regression of disease, diet plus cholestyramine therapy substantially diminished the rate of progression of lesions when the groups of patients who were designated as exhibiting definite or probable disease progression without regression were combined. Thus, 49% of patients in the placebo group exhibited definite or probable disease progression with no regression, as compared with only 32% of the cholestyramine-treated group.

The mixed-response category was not anticipated, but because of the requirement that at least two of the three panels observed both lesion regression and progression within a single patient, we do believe mixed response is a true phenomenon. The mixed response does not represent deterioration as unambiguously as does lesion progression alone. For this reason we choose to analyze the results two ways, both excluding those patients with mixed response from the progression group and then counting those patients with mixed response with those who had clear-cut progression. Since mixed response occurred more frequently among the cholestyramine-treated patients ($p = .22$ for a two-sided comparison), considering mixed response as progression diminished the effect of treatment.

When only lesions producing 50% or more luminal narrowing at entry into study were considered, 33% of the placebo group exhibited definite or probable progression, as compared with a progression rate of only 12% in the cholestyramine-treated group. This difference was significant at the .05 level. The significance of this latter finding must be viewed cautiously, since this subgroup had not been defined before initiation of the study. However, there is no mixed-response category in the subgroup and so the results are more definitive.

In the primary analysis the unit of disease status was considered to be the individual patient rather than the individual lesion. The basis for this stems from what we believe is a reasonable assumption: that lesions within a given patient do not change independently. These lesions are exposed to the same level of general risk factors associated with that particular patient (smoking, weight, age, blood pressure, and serum lipid levels). If changes in individual lesions are examined, however, results suggesting a salutary effect of diet plus cholestyramine therapy are again obtained (table 11). While all of the analyses presented in table 11 favor cholestyramine therapy, only one analysis (that for progression of lesions causing 50% or more stenosis) achieved nominal statistical significance.

The lack of consistently strong, statistically significant results indicating a benefit of cholestyramine therapy may reflect weak drug efficacy. On the other hand, the sample size was relatively small and did not reach the estimated 250 patients needed to approach a 90% chance of detecting a cholestyramine-induced change in the reduction rate of progression from 60% to 40%. Multivariate analyses, which adjust for those baseline characteristics unequally distributed at baseline, give supportive evidence that the beneficial effect of cholestyramine is real and significant ($p < .05$). Thus, although the results cannot be considered definitive, the evidence provided by this investigation suggests that lowering of cholesterol produced by diet and cholestyramine therapy inhibits the rate of progression of coronary obstructive lesions. Further evidence favoring this conclusion is provided by the companion article,[27] in which the effects of lowering plasma cholesterol levels, regardless of assigned treatment group, are analyzed.

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Article Title < Serial angiographic evidence of rapid resolution of coronary artery stenosis>

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the infants had increase in retractions five to ten minutes after onset of pH probe-documented reflux, suggesting that their upper airway obstruction had increased. Two of five infants treated medically and six of six treated surgically had resolution of their stridor within two days to three weeks. These temporal relationships are suggestive, but not incontrovertible, evidence of a causal relationship between gastroesophageal reflux and stridor. Our case is stronger proof of such a relationship.

Four logical alternative explanations could account for stridor and gastroesophageal reflux occurring together: 1) the reflux causes the upper airway obstruction (*eg*, by reflex laryngospasm with the sensory input either esophageal or laryngeal); 2) the upper airway obstruction causes the gastroesophageal reflux (*eg*, by excessive negative intrathoracic pressure overcoming a low esophageal sphincter pressure); 3) the upper airway obstruction and gastroesophageal reflux are both caused by a third phenomenon (episodic fluctuations in autonomic smooth muscle tone in the larynx and lower esophageal sphincter); and 4) the upper airway obstruction and gastroesophageal reflux occur together by chance alone. The fourth explanation is very unlikely because of the frequent, documented, clear relationship between the two phenomena in the 11 infants reported to date. The second and third explanations may contribute to the association between gastroesophageal reflux and stridor, although there is little specific evidence in their favor at present. The fact that the relief of the stridor followed the treatment of the reflux in all patients reported is strong evidence in favor of the first explanation. Our patient's repeated relief of stridor with spontaneous clearance of refluxed acid indicates that it was the acid clearance rather than any direct effect of a treatment that relieved the stridor.

Herbst et al[9] have documented laryngospasm as a response to intraesophageal instillation of acid in some infants. The exact mechanism of this response is unknown, but vagal reflexes have been implicated. Similarly, gastroesophageal reflux causing laryngospasm has been implicated in some instances of apnea and SIDS.[7-9,13]

Many people have gastroesophageal reflux, but only rarely does stridor result. All reported patients with gastroesophageal reflux and stridor have been infants, perhaps because their normally smaller upper airways predispose to stridor, or because laryngospasm as a reflex response to gastroesophageal reflux is the response of an immature nervous system. Three of these individuals, including our patient, had an upper airway anomaly (laryngomalacia or micrognathia) further predisposing to stridor, although apparently insufficient alone to cause it. The four other reported patients who underwent bronchoscopy had laryngeal inflammation, perhaps also a cause of airway narrowing. We suggest that stridor in infants with gastroesophageal reflux may only occur in infants who also have upper airway narrowing, which may be primary, or secondary to laryngeal inflammation caused by refluxed acid. Whether the contribution of the gastroesophageal reflux to laryngospastic events is mediated through vagal reflexes from the esophagus or through laryngeal aspiration is unknown, although several studies implicate the former.[5,8]

We recommend that gastroesophageal reflux, as well as causes of upper airway narrowing, be considered in patients with stridor.

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Serial Angiographic Evidence of Rapid Resolution of Coronary Artery Stenosis*

Timothy A. Sanborn, M.D.; David P. Faxon, M.D.; Mirle A. Kellett, M.D.; and Thomas J. Ryan, M.D.

An example of rapid, spontaneous resolution of an eccentric coronary luminal narrowing from 95 percent to 80 percent and subsequently to 50 percent stenosis over a six-week time period is presented. Spontaneous thrombolysis is proposed as the explanation for these changes and is discussed with reference to existing experimental and clinical observations.

Spontaneous resolution of coronary stenosis after myocardial infarction has been demonstrated previously;[1] however, the pathophysiology of this process remains unclear. The angiographic appearance of single or multiple thin

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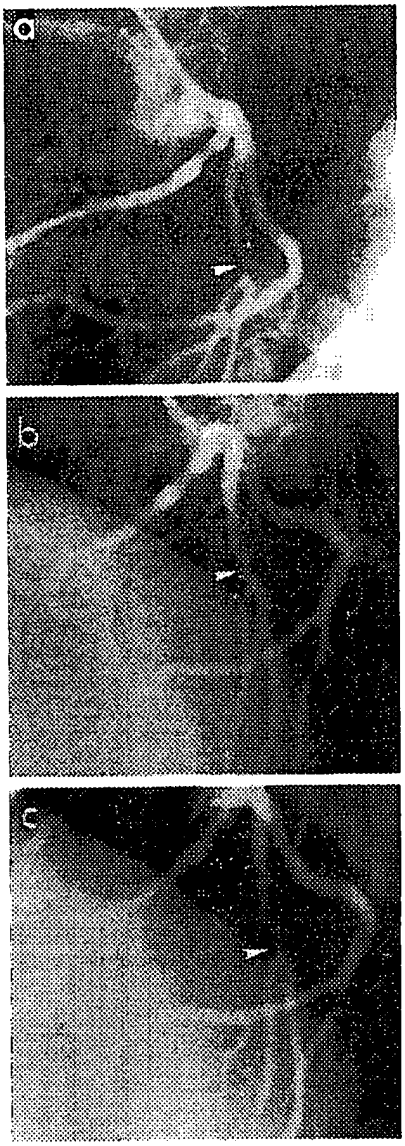

FIGURE 1a. Forty-five degree LAO-cranial view from the three catheterizations. On March 18, 1982, film reveals an eccentric 95 percent tubular stenosis in the ramus intermedius with delayed filling of the distal vessel noted on cineangiography. 1b. On March 29, film shows an 80 percent lesion with shortening of stenosis, loss of mural material proximal to the stenosis, and irregularities noted along the luminal surface. 1c. On May 3, film reveals further smoothing and resolution of the stenosis to 50 percent and a further loss of obstructing mural material.

channels at the site of prior total occlusion suggests a process of slow recanalization confirmed at autopsy.[2] Rapid resolution of total or subtotal intraluminal filling defects is suggestive of spontaneous intraluminal thrombolysis.[3] The radiographic appearance of resolving arterial wall irregularities and pouch formation in our patient suggest mural thrombolysis or dissolution of platelet aggregates.

CASE REPORT

A 50-year-old white man suffered a subendocardial myocardial infarction on March 9, 1982 documented by elevated cardiac enzymes and concurrent anterolateral ST-segment depression. His hospital course was complicated by postinfarction angina which was only partially responsive to maximal medical therapy with nitrates, propranolol (Inderal) and nifedipine. Because of continued anginal pain, the patient underwent cardiac catheterization on March 18, 1982 and was found to have a single eccentric lesion occluding 95 percent of the proximal ramus intermedius, which was unchanged after administration of nitroglycerin (Fig 1a). Due to his clinical status and single vessel disease, transluminal angioplasty was attempted on March 29, 1982. Angiography at this time revealed an 80 percent stenosis with an irregularity along the luminal surface suggesting loss of mural material (Fig 1b). Again, no angiographic change occurred with administration of intracoronary nitroglycerin. Angioplasty was unsuccessful due to inability to cannulate the origin of the ramus intermedius with the available catheter. The patient was discharged on therapy with his usual cardiac medications along with aspirin and dipyridamole. On May 3, 1982 (six weeks after the first angiogram), repeat angiography revealed a 50 percent obstruction with further smoothing and resolution of the luminal irregularities unchanged by intracoronary nitroglycerin (Fig 1c). On this occasion, the lesion was easily passed with a Gruentzig 20-30C dilation catheter revealing a mean gradient of 17 mm Hg. The lesion was successfully dilated at this time to 20 percent residual stenosis and no residual gradient.

DISCUSSION

This patient demonstrates rapid spontaneous resolution of eccentric coronary luminal narrowing over a six-week period. Possible explanations for these changes include technical differences, spasm, recanalization, or spontaneous thrombolysis. Technical differences between studies are unlikely, as excellent filling occurred and at least three equivalent views of the vessel were taken during each study (30° RAO, 45° LAO cranial, and 60° LAO views). Coronary spasm is unlikely in view of the concurrent nifedipine and nitrate therapy and the lack of a response to intracoronary nitroglycerin. Recanalization, although possible, also seems unlikely since the entity is characterized angiographically by multiple small channels which gradually enlarge over several months or years.[2] The angiographic resolution of irregularities along the luminal surface and the observation of a pouch in the arterial wall in this case is also different from that noted with subtotal[3] or total[4] intraluminal filling defects. The angiographic appearance in this case is more suggestive of a process of intra- or extramural thrombolysis or dissolution of platelet aggregates on the arterial wall. Indeed, experimental studies in a canine model suggest that platelet aggregates may play a role in spontaneous flow reduction and resolution noted in association with arteriographic lumen narrowing.[5] It remains unclear how often resolution of coronary stenosis occurs after myocardial infarction and to what extent thrombolytic, anticoagulant or antiplatelet medication may play a role.

In summary, the present case demonstrates rapid radiographic resolution of coronary arterial narrowing suggestive of mural thrombolysis or platelet aggregate dissolution rather than recanalization[2] or intraluminal thrombolysis[3,4] reported previously. The factors responsible for spontaneous lysis as opposed to further thrombosis and reocclusion are unknown and require further investigation in order to understand the pathophysiology of coronary stenosis after myocardial infarction. This is particularly important in deciding which patients require angioplasty to prevent reocclusion of a high-grade stenosis remaining after acute streptokinase infusion for myocardial infarction.[6]

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Bilateral Vocal Cord Paralysis for 26 Years with Respiratory Failure*

Timing of Restoration of Tidal Volume and Serum Electrolytes after Tracheostomy

Richard E. Kanner, M.D., F.C.C.P.

A 31-year-old man had respiratory failure caused by bilateral vocal cord paralysis. He had had limited exercise tolerance since the age of five years, when he had had poliomyelitis. Respiratory failure was present for at least three months. Following relief of the upper airway obstruction by tracheostomy, the patient's tidal volume increased from 200 ml to 500 ml in two days, his carbon dioxide tension fell from 75 to 38 mm Hg, and his arterial bicarbonate level decreased from 39.8 to 25.6 mEq/L in five days. The patient is currently doing well with a permanent tracheostomy.

Upper airway obstruction is an established cause of respiratory failure and cor pulmonale[1,2] and is usually noted in children who have enlarged tonsils and adenoids as the cause of the problem. Bilateral vocal cord paralysis is a less common and less well-described cause for upper airway obstruction which leads to respiratory failure. This report describes an adult with bilateral vocal cord paralysis for 26 years, with respiratory failure for at least three months who had reversal of his ventilatory difficulties following tracheostomy. The patient also demonstrates the rapidity of the return to normal of the sensitivity of the respiratory center and serum bicarbonate level once the obstruction was relieved.

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Case Report

A 31-year-old man was referred to the University of Utah Medical Center with difficulty in breathing. He had a history of bulbar poliomyelitis at the age of five years, with therapy in a tank respirator for six months. Sequellae included a hoarse voice and limitation of physical activities due to dyspnea. The patient complained of mild problems with swallowing. At the age of 28 years, he moved from sea level to 1,500 m and then developed more pronounced dyspnea which progressed. A "flu-like" illness three months before admission resulted in a marked loss of energy and an inability to work in his cabinet-making shop. Over a six-month period the patient lost 18 kg (40 lb) of weight and had increasing difficulty in sleeping at night, with hypersomnia during the day. His wife witnessed apneic episodes during sleep and myotonic jerks which occurred several times per hour. Also, the patient exhibited inappropriate behavior, such as pretending to comb his hair without a comb or being in a shower while sitting in bed. Bilateral vocal cord paralysis was diagnosed, and hypoxemia was documented; the patient was started on oxygen therapy at home plus digoxin for heart failure. He was also receiving salicylazosulfapyridine (sulfasalazine) for an unspecified type of colitis. The patient was a lifelong nonsmoker.

On physical examination the patient was a mildly obese man who had labored respirations and a hoarse hard-to-understand voice. His pulse rate was 116 beats per minute, his blood pressure was 140/70 mm Hg, and his respiratory rate was 24/min. The hemidiaphragms barely moved when assessed by percussion, and breath sounds were diminished. A grade 2/6 systolic ejection murmur was present. The fingers and mucous membranes were cyanotic. No edema was detected. About two or three times per hour, myotonic jerks of the upper body were noted. Direct laryngoscopic examination revealed no motion of the vocal cords with speech; and with a strong inspiratory effort, they were drawn down into the trachea as if they were a continuous membrane with a barely perceptible opening being present. The hematocrit reading was 43 percent. The chest roentgenogram showed an increased size of the pulmonary outflow tract; chest fluoroscopic examination disclosed decreased motion of the hemidiaphragms. The electrocardiogram showed nonspecific

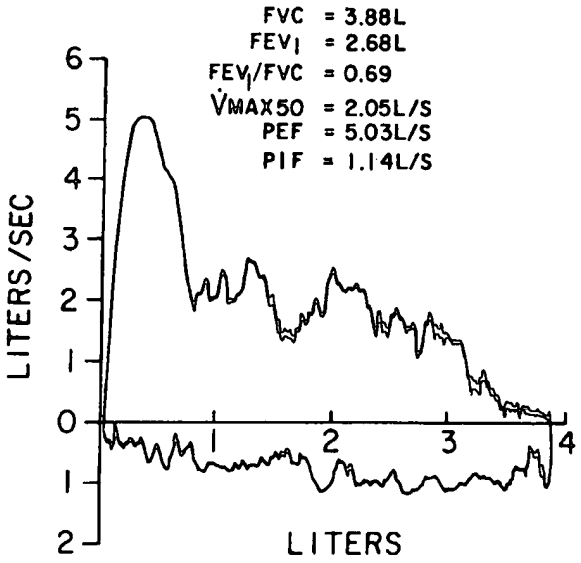

FIGURE 1. Maximal expiratory flow-volume curve, demonstrating "plateau" on both inspiration and expiration consistent with large airways obstruction. Inspiratory flow is more markedly reduced than expiratory flow, indicating obstruction is above the thoracic inlet. FVC, Forced vital capacity; FEV_1, forced expiratory volume in one second; Vmax 50, maximum expiratory flow at 50 percent of vital capacity; PEF, peak expiratory flow; and PIF, peak inspiratory flow.

AHA Medical/Scientific Statement

Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease

Writing Group

Neil J. Stone, MD

Footnotes

Reducing intake of saturated fat and dietary cholesterol and avoiding excess calories, which can lead to obesity, remain the cornerstore of the dietary approach to decreasing risk of atherosclerotic vascular disease. During the past 20 years, however, there has been renewed interest in other dietary components that might favorably improve lipid profiles and reduce risk of coronary heart disease (CHD). Fish and fish oil, rich sources of omega-3 fatty acids, have sparked intense interest in both epidemiological studies, which suggest a favorable effect on CHD, and metabolic ward studies, which show a striking improvement in lipid profiles in hyperlipidemic patients. Confusion has resulted from clinical trials of fish fish oil in patients with CHD, which did not corroborate early observational findings, and newer results, which suggest clinical benefit due to a mechanism independent of lipid effects.

What Are Omega-3 Fatty Acids?

Fish and other marine life are rich sources of a special class of polyunsaturated fatty acids known as the omega-3 or n-3 fatty acids.[1,2] They are so named because the first of the several double bonds occur three carbon atoms away from the terminal end of the carbon chain. The three n-3 polyunsaturated fatty acids (n-3 PUFAs) are alpha linolenic acid (LNA), eicosapentenoic acid (EPA), and docosahexenoic acid (DHA). LNA is an 18-carbon chain fatty acid with three double bonds; in the form of tofu, soybean, and canola oil and nuts, it is an important plant-based source of n-3 PUFA for vegetarians and non-seafood eaters. EPA and DHA are very long-chain fatty acids obtained from marine sources. These, along with n-6 polyunsaturated fatty acids (n-6 PUFAs) that cannot be synthesized from nonlipid precursors such as linoleic acid, are considered essential fatty acids that must be

consumed in the diet. The n-6 PUFAs are obtained primarily from plant sources, especially seeds. Arachidonic acid is a long-chain n-6 PUFA that is found in meats, fish, and plants or is synthesized from linoleic acid. Arachadonic acid and marine lipids both serve as key intermediates for eicosanoids like thromboxanes and prostacyclins, which are important for platelet and vessel wall physiology.

Fish Intake and Risk Factors

Effects of Omega-3 Fatty Acids and Lipoproteins

The addition of omega-3 fatty acids to the diet lowers triglyceride levels, an effect that is pronounced in those with marked hypertriglyceridemia.[3] The triglyceride-lowering effect is not seen with plant sources of n-3 PUFA.[4] In those patients with type V hyperlipidemia, the use of fish oil supplements is an important therapeutic option.[5] Connor[6] listed the following putative mechanisms of dietary n-3 PUFA on lipoprotein metabolism in humans: (1) inhibition of VLDL triglyceride synthesis, (2) decreased apoprotein B synthesis, (3) enhancement of VLDL turnover with an increased fractional catabolic rate of VLDL, (4) depression of LDL synthesis, and (5) reduction of postprandial lipemia.

A critical review by Harris[2] has clarified the discrepancy among fish oil studies reporting effects on LDL cholesterol (LDL-C). He noted that in the majority of studies reporting reductions in LDL-C levels, the saturated fat intake was lowered when subjects switched from the control diet to the fish oil diet. When fish oil is consumed and saturated fat intake is constant, LDL-C levels either do not change or may increase.

Although fish oil is not recommended in the treatment of hypercholesterolemia, it does have a role in the treatment of lipoprotein disorders characterized by severe hypertriglyceridemia. It can be quite useful in those severely hypertriglyceridemic (triglyceride >1000 mg/dL) patients for whom attempts to correct secondary causes (through diet, exercise, and gemfibrozil) have proved inadequate.[7] Although a negative aspect is the concomitant elevation in LDL-C that occurs when fish oils are given to these patients with lower plasma levels of triglyceride, this is usually not a problem for those with severe hypertriglyceridemia, because LDL-C values are usually quite low. It can be a problem for those with more modest elevations of triglycerides in whom the elevation of LDL-C will actually move the patient away from the desired LDL-C goal.

Fish oil supplementation does not appear to impair glucose tolerance in nondiabetic coronary bypass patients.[8] Among diabetics, initial studies showed deterioration of glucose tolerance with fish oil consumption.[9] Nonetheless, Connor and coworkers[10] designed a longer term study in which body weights were unchanged between fish oil and olive oil groups and no deterioration in glucose homeostasis was demonstrated in those individuals with diabetes. Westerveld and colleagues[11] conducted a randomized, blinded, placebo-controlled trial that also documented reduced platelet aggregation as well as triglyceride lowering in the fish oil group. In both trials the fall in triglyceride level was accompanied by a rise in LDL-C similar to that seen in studies of patients with combined hyperlipidemia.[12] This rise in LDL-C level was not seen when a low dose of omega-3 fatty acids was given to 20 ambulatory subjects with non-insulin-dependent diabetes mellitus in a randomized, double-blind, prospective, controlled clinical trial.[13] Although sample size

may have been inadequate to show an LDL-C effect, fish oil significantly inhibited platelet aggregation and thromboxane A_2 production, while it reduced triglyceride levels by 44 mg/dL and decreased upright systolic blood pressure by 8 mm Hg compared with safflower oil. Finally, a recent study looking at vascular reactivity suggested that fish oil ingestion in diabetics could favorably alter arterial wall compliance without affecting fasting blood sugar, cholesterol, or blood pressure.[14] Clearly, further research on the use of n-3 PUFA in diabetics is required.

Effect of Omega-3 Fatty Acids on Hypertension

A meta-analysis of placebo-controlled studies showed that fish oil reduced blood pressure in in a dose-response fashion in those with hypertension and hypercholesterolemia but not in those participants with normal blood pressures.[15] The effects were small, and it is not clear whether this effect is sustained over the long term.

Effect of Omega-3 Fatty Acids on Coagulation Profiles

A concise review of studies on the prevention of thrombosis in laboratory animals and in humans emphasized the important role of n-3 PUFA, which affects cellular responses in platelets, monocytes, and endothelial cells.[16] The reduced platelet aggregation and prolonged bleeding times of the Greenland Eskimos suggested an important mechanism by which n-3 PUFAs could affect CHD.[17] When bleeding times are measured, the effects of fish oil are additive to those of aspirin.[18] Studies in swine fed high cholesterol diets with and without cod liver oil showed that there was less coronary atherosclerosis in the cod liver oil group but that there was no relationship to lipid changes. The pigs fed cod liver oil had significant decreases in serum thromboxane B_2 levels and increases in platelet fatty acid deposition of EPA.[19] Fish oil supplements increased levels of tissue plasminogen activator (TPA) and decreased concentrations of plasminogen activator inhibitor, both enhancers of fibrinolysis.[20] One study comparing fish oil with rapeseed oil noted that fish oil decreased lipoprotein(a) by 14%.[21] This effect was not seen in all male subjects who were hospitalized with CHD but did correlate with a large reduction in TPA. The Atherosclerosis Risk in Communities study compiled data from four US communities (15000 participants, both black and white) on six hemostatic factors: fibrinogen, factor VII, factor VIII, von Willebrand factor, protein C, and antithrombin III.[22] These were communities not known for their high intake of fish. Dietary intake of n-3 PUFA showed negative associations with levels of fibrinogen, factor VIII, and von Willebrand factor and a positive association with protein C (whites only). These findings may help explain, in part, the reduced incidence of vein graft occlusion seen in patients after coronary artery bypass grafting who receive n-3 PUFA.[23] In a randomized controlled trial of dietary supplementation with n-3 fatty acids in bypass patients who received usual anticoagulation with aspirin or warfarin, an inverse relation between relative change in serum phospholipid n-3 fatty acids and vein graft occlusions was observed. Thus, the prevention of thrombosis remains a promising area for n-3 PUFA research.

Effect of Omega-3 Fatty Acids on Immune Response

The potent anti-inflammatory effects of fish oils and their effects on the immune response are beyond the scope of this review. Worthy of mention are the detailed studies of Meydani

et al[24] on immune responses seen with dietary fish supplementation. They showed decreased cell-mediated immunity when the Step II National Cholesterol Education Program (or AHA) diet was supplemented with a high fish intake as compared with one low in fish intake (121 to 188 g of fish per day versus 33 g of fish per day). The clinical significance of this important finding needs further investigation.

Fish Intake and CHD

Observational Studies

Early studies of Greenland Eskimos (Inuit) highlighted their lower coronary mortality compared with their Danish counterparts. The Eskimos' diet included a strikingly higher intake of n-3 PUFAs rich in marine sources such as seal and whale that resulted in lower blood cholesterol, lower triglycerides, lower LDL-C, lower VLDL cholesterol, increased HDL cholesterol, increased bleeding times, and lower rates of CHD. In addition, prospective epidemiological studies from the Netherlands, Chicago, and the Multiple Risk Factor Intervention Trial confirmed that men who ate at least some fish per week had a lower mortality from CHD than those men who ate none.[25-28] On the other hand, two studies describing populations with high intakes of fish did not show such a beneficial effect.[29,30]

Clinical Trials

There is no convincing role for fish oil supplements in the prevention of CHD. The strongest evidence indicating a beneficial effect of fish intake on CHD came from the Diet and Reinfarction Trial (DART), in which men who were instructed to eat fish after myocardial infarction (MI) had a 29% decline in all-cause mortality as compared with those in the placebo group.[31] No significant lowering of cholesterol was seen, and very few men were taking aspirin. Yet the Health Professionals Follow-up Study,[32] a large-scale prospective cohort study, reported no association between increasing fish intake and CHD. The authors concluded that increasing fish intake beyond one or two servings per week is not likely to improve the primary prevention of CHD.

A nested case-control study was conducted among the 14916 participants in the Physicians' Health Study.[33] Each participant with MI was matched by smoking status and age with a randomly chosen control participant who had not developed CHD. Fish oil intake was estimated by measuring plasma levels in cholesterol esters and phospholipids. No association was found between fish oil levels and the incidence of MI even when results were adjusted for major cardiovascular risk factors. Although early trials suggested that fish oil held some promise if ingested early before angioplasty, a clinical trial large enough to find a significant effect did not, despite a dose of 8 g/d of n-3 PUFA.[34] This trial did document the safety of fish oil supplementation without any evidence of excess bleeding in the patients who all took aspirin. Moreover, a clinical trial with angiographic end points showed that among normocholesterolemic men with CHD, fish oil treatment (6 g n-3 PUFA for 2 years) did not produce significant changes in the diameter of the coronary arteries.[35]

Effects of Omega-3 Fatty Acids on Sudden Death

DART peaked interest in whether a diet rich in fish oil could reduce risk of sudden death

because of the striking difference in sudden deaths seen early in the trial, suggesting a possible action on either thrombosis or arrhythmic death rather than on atherosclerosis.[9] Support for the latter hypothesis came from the Lyon Trial,[36] which compared a "Mediterranean-type" diet rich in LNA with the AHA Step I diet in patients with known MI. Although no improvement in lipids, lipoproteins, and body mass index was seen, there was a striking difference in mortality, with eight sudden deaths in the control group and none in the alpha LNA-rich diet group. The risk ratio of cardiac death was 0.19 (95% CI, 0.06 to 0.65), with $P<.002$. These findings were extended by the carefully done population-based case-control study from Seattle and King County, Washington.[37] Among 334 patients with primary cardiac arrest, the intake of n-3 PUFA per month was significantly less than that seen in age- and sex-matched community controls. The data suggested that an intake of 5.5 g of n-3 PUFA per month (equivalent to one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest after adjustment for potential confounding factors. Moreover, studies of red blood cell membrane n-3 PUFA in both patients and controls allowed calculation of risk based on this sensitive parameter of dietary n-3 PUFA intake. These findings were consistent with experimental evidence suggesting that the n-3 PUFAs have an important effect on vulnerability to ventricular fibrillation in the the setting of myocardial ischemia.[38] Of additional interest are recent data showing suppression of premature ventricular contractions (PVCs) in middle-aged patients with frequent PVCs randomly assigned to take either fish oil (as cod liver oil containing 2.4 g of n-3 PUFA) or sunflower seed oil.[39] Clearly, further studies are needed to explore the potential of fish oil in the prevention of sudden cardiac death.

Conclusions

When considering cardiovascular health, it seems premature to recommend general usage until compelling evidence for the beneficial action of fish oil supplements is at hand. Although doses of 3 to 8 g of n-3 PUFA per day in those with CHD were not associated with significant adverse effects in recent clinical trials,[8,34] evidence for beneficial effects in CHD patients is either lacking or needs additional study. Currently, fish oil capsules can only be recommended for the infrequent patients with severe, treatment-resistant hypertriglyceridemia who are at increased risk for pancreatitis. Potential side effects should be kept in mind (Table[1,40]). On the other hand, inclusion of marine sources of the n-3 PUFA in the diet seems reasonable because they are good sources of protein without the accompanying high saturated fat seen in fatty meat products. Moreover, as Harris has noted, the potential for benefit remains high, since dietary fish oils affect "a myriad of potentially atherogenic processes."[41] This requires the continued support of cardiovascular research on the n-3 PUFA.

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Table. Potential Side Effects of Fish Oil Capsules[1,37,38,40]

General:	Fishy odor, gastrointestinal upset
Coagulation:	Increased bleeding time may result in nosebleeds, easy bruising
Metabolism:	Can increase cholesterol in those with combined hyperlipidemia
	Can increase calorie intake and hence weight gain
	Some preparations have added cholesterol
	Some lack vitamin E (alpha tocopherol); concern for oxidation
Immune response:	Various parameters are decreased (uncertain significance)
Toxicity:	Vitamin A and D toxicity with some preparations
	Some fish oils (not highly refined) may contain pesticide
	Concerns regarding effects on immune response
Cost:	Expensive compared with dietary fish intake

"Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease" was approved by the Science Advisory and Coordinating Committee of the American Heart Association in July 1996.

(*Circulation.* 1996;94:2337-2340.)

Patient Level Information

FISH OIL

AHA Recommendation

We recommend eating **fish** two times per week. Fatty **fish** like mackerel, lake trout, herring, sardines, albacore tuna and salmon are also high in omega-3 fatty acids, which may have health benefits. **Fish** are a good source of protein without the high saturated fat found in fatty meat products.

The benefits and risks of eating fish oil still need to be defined by further research. Until there's compelling evidence that fish oil supplements (capsules) benefit overall cardiovascular health, we don't recommend their general use.

Using fish oil capsules to lower high blood cholesterol levels is not recommended. These capsules may be recommended for patients with severely high triglycerides (tri-GLIS'er-ídz) and patients with pancreatitis (pan"kre-ah-TI'tus) (inflammation of the pancreas).

Background

Since the previous American Heart Association Science Advisory, "**Fish** Consumption, **Fish Oil**, Lipids and Coronary Heart Disease," important new findings have been reported about the beneficial effects of omega-3 fatty acids on cardiovascular disease. These include evidence from randomized, controlled clinical trials. New information has emerged about how omega-3 fatty acids affect cardiac function (including antiarrhythmic effects), hemodynamics (cardiac mechanics) and arterial endothelial function. It helps clarify potential mechanisms of action.

Compelling evidence shows that increasing omega-3 fatty acid intake benefits patients with preexisting cardiovascular disease as well as healthy people, especially within the context of a diet that meets our dietary guidelines.

What are omega-3 fatty acids?

In omega-3 fatty acids, the first of the double bonds between carbon atoms occurs three carbon atoms away from the end of the carbon chain. There are three omega-3 fatty acids:

alpha-linolenic (lin"o-LEN'ik) **acid** (LNA) -- found in tofu, soybean and canola oils and nuts.

eicosapentenoic (i-KO'sa-pen-ten-O'ik) **acid** (EPA) -- found in seafood, especially cold-water **fish** and seafood.

docosahexenoic (do-KO'sa-hecks-en-O'ik) **acid** (DHA) -- found in seafood, especially cold-water **fish** and seafood.

What do epidemiological and observational studies show?

Coronary Heart Disease

Three prospective epidemiological studies reported that men who ate at least some **fish** weekly had a lower coronary heart disease mortality than men who ate none. More recent evidence has been reported in a 30-year follow-up of the Chicago Western Electric Study. It showed that eating **fish** favorably affects coronary heart disease mortality, especially nonsudden death from myocardial infarction (heart attack). Men who ate 35 g or more of **fish** daily compared with those who consumed none had a relative risk of death from CHD of .62 and a relative risk of nonsudden death from myocardial infarction of .32. (A relative risk of less than 1.00 indicates a lower risk than the comparison population.)

In an ecological study, **fish** consumption was linked with a reduced risk from all-cause, ischemic heart disease and stroke mortality in 36 countries. Also, a study of Japanese living in Japan or Brazil reported a dose-response relationship between the frequency of weekly **fish** intake and reduced CVD risk factors (i.e., obesity, hypertension, glycohemoglobin and ST-T segment change on the electrocardiogram).

Fish Oil

Several investigators have reported on the beneficial effects of increased omega-3 fatty acid intake in patients with coronary heart disease. Several of these studies used supplements containing long-chain omega-3 fatty acids (EPA and DHA, or "**fish oil**") at doses ranging from 850 mg to 2.9 g/day. Other studies have shown that higher doses (3-4 g/day) provided as supplements can reduce plasma triglyceride levels in patients with hypertriglyceridemia. High intakes of fatty **fish** (one serving per day) can result in intakes of EPA and DHA of about 900 mg/day. Further studies are needed to establish optimal doses of omega-3 fatty acids (including EPA, DHA and alpha-linolenic acid) for both primary and secondary prevention of coronary disease as well as the treatment of hypertriglyceridemia.

For secondary prevention, beneficial effects of a high dose of omega-3 fatty acids on recurrent events have been reported in the CISSI trial. A 20 percent reduction in overall mortality and a 45 percent reduction in sudden death after 3.5 years was reported in subjects with preexisting CHD (who were being treated with conventional drugs). They were given 850 mg of omega-3 fatty acid ethyl esters (as EPA and DHA) either with or without vitamin E (300 mg/day).

Other studies have demonstrated beneficial effects of omega-3 fatty acids, EPA and DHA (1.9

g/day) and alpha-linolenic acid (.8 percent of energy) in subjects with CHD. Consuming one fatty acid meal per day (or alternately, a **fish oil** supplement) could result in an omega-3 fatty acid intake (EPA and DHA) of about 900 mg/day. This amount is shown to beneficially affect CHD mortality in patients with coronary disease.

For more detailed research, see:

- AHA Science Advisory: **Fish** Consumption, **Fish Oil**, Lipids, and Coronary Heart Disease, #71-0096 *Circulation.* 1996;94:2337-2340
- AHA Scientific Statement: AHA Dietary Guidelines: Revision 2000, #71-0193 *Circulation.* 2000;102:2284-2299; *Stroke.* 2000;31:2751-2766

Related AHA publication(s):

- An Eating Plan for Healthy Americans... American Heart Association Diet
- Easy Food Tips for Heart-Healthy Eating (also in Spanish)

See also in this Guide:

- **Cholesterol**
- **Cholesterol**, Lowering the Levels
- Diabetes Mellitus
- Dietary Guidelines for Healthy American Adults
- Dietary Guidelines for Healthy Children
- Fat
- Fat Substitutes
- Fats and Oils
- High Blood Pressure
- Obesity
- Step I and Step II Diets
- Sudden Cardiac Death
- *Trans* Fatty Acids
- Triglycerides

See also in this Web site:

- AHA Dietary Recommendations

AHA Scientific Statement:

- **Fish** Consumption, **Fish Oil**, Lipids, and Coronary Heart Disease
- AHA Dietary Guidelines: Revision 2000

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ARTICLES

Modulation of fibrinolytic response to venous occlusion in humans by a combination of low-dose aspirin and n-3 polyunsaturated fatty acids

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Aspirin at high but not at low doses reduces the fibrinolytic response to venous occlusion. Inhibition of vascular prostacyclin synthesis could be involved in this effect. Fish oil supplementation may redirect prostanoid metabolism toward an overall "antithrombotic" condition but with controversial effects on prostacyclin formation. In this study we investigated the effect of low-dose aspirin together with n-3 polyunsaturated fatty acid (PUFA) supplementation on the fibrinolytic response to venous occlusion. Following a double-blind, randomized, crossover design, six healthy volunteers (three men and three women, 24- 37 years old) were given for 29 days 5.3 g eicosapentaenoic and docosahexaenoic acids or a corresponding dose of n-6 PUFAs as control; aspirin (40 mg/day) was then added for an additional 14 days. A 2-month washout period was allowed before the crossover. Blood was collected before and after venous stasis on days 0, 29, and 43 of each test period. A combination of aspirin with n-3 PUFAs reduced the fibrinolytic response to venous occlusion in all subjects, the mean value of fibrinolytic activity after stasis being 240 +/- 40 mm2, a value significantly lower than at baseline (366 +/- 51 mm2, mean +/- SEM, $p < 0.05$). Similarly, the tissue-type plasminogen activator (t-PA) antigen level was lower in the aspirin + PUFA-treated group. Plasminogen activator inhibitor activity before stasis was enhanced by n-3 PUFA supplementation (from 7.5 +/- 2 to 14.8 +/- 3 IU/ml, $p < 0.05$), an effect not affected by aspirin.(ABSTRACT TRUNCATED AT 250 WORDS)

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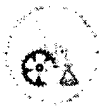

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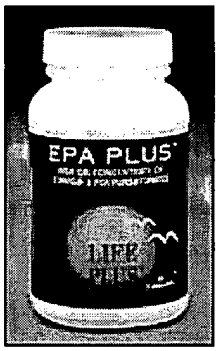

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EPA PLUS™ is a natural marine lipid concentrate, providing a dietary source of the valuable Omega-3 fatty acids, Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA). Recent nutritional research has revealed important new evidence that a concentration of these marine lipids in the diet improve overall health by helping to nutritionally support the natural control of blood lipids, such as cholesterol.

This helps to protect against heart disease, improve endocrine functions and at the same time support many enzyme functions in the body, which play a key role in neurological functions as well. The Eskimos and other societies with diets rich in fish are known to have a greatly reduced incidence of heart and circulatory disease and it is thought that supplementing with high quality EPA and DHA like that found in Life Plus EPA PLUS can help prevent heart disease.

EPA & DHA

Eicosapentaenoic Acid (EPA) is a member of the Omega-3 fatty acid family. EPA is required for the production of a special group of substances in the body called prostaglandins, which control blood clotting and other arterial functions. EPA also provides a natural approach to lower blood cholesterol and triglycerides.

Of almost equal importance, but not as widely researched, is Docosahexaenoic Acid (DHA), a major component of the human brain tissues and the retinal tissues of the eyes. It also serves the other important function of the transmission of nerve impulses in the nervous nervous system.

EPA PLUS supplies these important fatty acids in the highest concentrations found and, in addition, it does not contain potentially harmful levels of Vitamins A and D, such as that found in equivalent amounts of many other fish liver and fish body oils.

Suggested Use:

One to two capsules two or three times per day with meals.

Contains no preservatives, sugar, starch, salt, wheat, yeast, corn, milk, soy derivatives, artificial flavoring or

coloring agents.

FISH OILS

The relationship between fish oils and therosclerosis appears to be an intimate one. The higher the consumption of fish, the lower the risk of dying from coronary heart disease. In people with coronary heart disease, fish oils may reduce the risk of thrombosis, reduce the pain of angina and improve cardiac function. There is even preliminary evidence that they may inhibit the development of atherosclerosis.

According to studies published in the well respected British scientific journal, Lancet, the incidence of heart disease related to atherosclerosis, including coronary artery disease, in Greenlandic Eskimos is extremely low. From 1963 to 1967 only three cases of these diseases were reported in the entire Eskimo population of Greenland. Moreover, not a single established case of diabetes is known to have been reported in the population of the Greenlandic Uhanak district. Since diabetes and heart disease affected literally millions of Americans in the 1980's and 1990's, the lack of heart disease in Eskimos and other societies has attracted the serious attention of many scientists around the world.

The food of the Greenlandic Eskimos consists largely of meat from whales, seals, sea birds and fish (usually halibut and salmon). Needless to say, their food is extremely rich in protein and fat and low in carbohydrates, but it is extremely high in the Omega-3 Polyunsaturates EPA and DHA as contained in Life Plus EPA PLUS.

EPA

Doctors have been saying for years that large amounts of fat in the diet can lead to heart disease and other disorders. Why, therefore, can a group of people who consume such large amounts of protein and fat have such low incidence of atherosclerotic heart disease? Until recently, scientists have been baffled by this important question. The new link in their chain of understanding now centers around a marine lipid concentrate, containing Eicosapentaenoic Acid (EPA).

EPA is a direct source of an important substance called prostaglandin E3. Prostaglandin E3 is directly responsible for making blood platelets (cells which form a "plug" wherever an injury occurs) less sticky, thus leading to an easier flow of blood throughout our bodies. This natural antithrombotic "anti-clotting" effect of EPA has been well researched. This means that EPA is intimately involved in bodily processes that inhibit blood clots (obstructions to circulation), particularly in the small capillaries of the heart. When a small blood vessel is injured, platelets adhere to each other around the edges of the injury, forming a clot. This is a natural protective mechanism that prevents us from literally bleeding to death.

However, when platelets in the blood become too sticky, they can clump abnormally fast and too frequently. This rapid and extensive platelet clumping can actually inhibit circulation and be a major contributor to heart and circulatory disease.

DHA

Of almost equal importance, but not as widely researched, is Docosahexaenoic Acid (DHA). It comprises a significant amount of the tissue, which makes up our brains as well as a large part of the retina of the eye.

The average American diet is very low in fresh fish and derivatives of sea food that contain EPA and DHA. On the other hand, it is high in refined carbohydrates and saturated fats. This kind of diet can lead to a serious deficiency in the raw materials necessary for proper platelet function in our blood stream. Recent dietary studies suggest that marine lipid complexes that contain EPA and DHA can have a very significant effect on lowering unwanted "blood fats." They may prove to be extremely useful natural substances powerful enough to normalize the high cholesterol and triglyceride levels that are so extensive in our modern American population.

Supplementing with EPA PLUS is a rational approach to naturally increasing the amount of Eicosapentaenoic Acid and Docosahexaenoic Acid in our daily diets. This product represents a significant advantage over other marine oils, which can supply a potentially toxic amount of Vitamins A and D, while supplying lower amounts of EPA and DHA factors.

HOW TO TAKE EPA PLUS

It is recommended to take one or two capsules with the two major meals each day. Many individuals also take EPA PLUS with the third meal as well. It is wise to limit the amount of saturated fat in your diet and increase the amount of high quality cold water fish.

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